Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2018-B-246 Radium-223-dichlorid

Stand: Januar 2019

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Radium-223-dichlorid
Zur Behandlung von Erwachsenen mit kastrationsresistentem, metastasierten Prostatakarzinom, welche zwei vorherige Therapien erhalten haben oder nicht für eine systemische Therapie geeignet sind

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	• Strahlentherapie
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschluss vom 29. März 2012 über eine Änderung der AM-RL: Anlage XII – Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Abirateronacetat: - Patientengruppe Best-Supportive-Care: Hinweis auf einen beträchtlichen Zusatznutzen. Beschluss vom 04. Juli 2013 über eine Änderung der AM-RL: Anlage XII – Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Abirateronacetat (neues Anwendungsgebiet): - Hinweis für einen beträchtlichen Zusatznutzen gegenüber dem abwartenden Vorgehen unter Beibehaltung der bestehenden konventionellen Androgendeprivation Beschluss vom 19. Juni 2014 über eine Änderung der AM-RL: Anlage XII – Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Radium-223 dichlorid: - Patienten, für die eine Behandlung mit Docetaxel infrage kommt: Ein Zusatznutzen ist nicht belegt gegenüber Docetaxel in Kombination mit Prednison oder Prednisolon - Patienten, für die eine Behandlung mit Docetaxel nicht infrage kommt: Hinweis für einen beträchtlichen Zusatznutzen gegenüber Best-Supportive-Care Beschluss vom 20.02.2014 über eine Änderung der AM-RL: Anlage XII – Beschlüsse über die

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Radium-223-dichlorid **Zur Behandlung von Erwachsenen mit kastrationsresistentem, metastasierten Prostatakarzinom, welche zwei vorherige Therapien erhalten haben oder nicht für eine systemische Therapie geeignet sind**	
Kriterien gemäß 5. Kapitel § 6 VerfO	
	Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Enzalutamid: - Patientengruppe Best-Supportive-Care: Hinweis auf einen beträchtlichen Zusatznutzen. Beschluss vom 18.06.2015 über eine Änderung der AM-RL: Anlage XII – Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Enzalutamid (neues Anwendungsgebiet): - Patientengruppe beobachtendes Abwarten: Hinweis auf einen beträchtlichen Zusatznutzen. Beschluss vom 29. März 2012 über eine Änderung der AM-RL: Anlage XII – Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Cabazitaxel: - Patientengruppe Best-Supportive-Care: Hinweis auf einen geringen Zusatznutzen. Beschluss vom 19. Juni 2008 über eine Änderung der Richtlinie Methoden Krankenhausbehandlung in Anlage II (Methoden, deren Bewertungsverfahren ausgesetzt sind): -Protonentherapie beim Prostatakarzinom
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Radium-223-dichlorid V10XX03 Xofigo®	Zugelassenes Anwendungsgebiet (28. September 2018): Xofigo wird als Monotherapie oder in Kombination mit einem LHRH-Analogon (LHRH: Lutei-nisierendes-Hormon-freisetzendes Hormon) zur Behandlung von erwachsenen Patienten mit metastasiertem kastrationsresistentem Prostatakarzinom (mCRPC) und symptomatischen Knochenmetastasen ohne bekannte viszerale Metastasen angewendet, bei denen die Er-krankung nach Erhalt von mindestens zwei vorausgehenden systemischen Therapielinien zur Behandlung des mCRPC (außer LHRH-Analoga) fortschreitet, oder für die keine andere verfügbare systemische mCRPCTherapie geeignet ist (siehe Abschnitt 4.4).
Antiandrogene	
Bicalutamid L02BB03 Bicalutamid-ratiopharm® 50 mg	Fortgeschrittenes Prostatakarzinom - Behandlung des fortgeschrittenen Prostatakarzinoms in Kombination mit einer LHRH-(Luteinisierendes-Hormon-Releasing-Hormon)-Analogon-Therapie oder einer operativen Kastration. […]
Flutamid L02BB01 Flutamid-biosyn®	Zur Behandlung von Patienten mit fortgeschrittenem Prostatakarzinom, bei denen eine Suppression der Testosteronwirkungen indiziert ist. Initialtherapie in Kombination mit einem LH-RH-Analogon oder in Verbindung mit Orchiektomie (komplette Androgenblockade) sowie bei Patienten, die bereits mit einem LH-RH-Analogon behandelt werden bzw. bei denen bereits eine chirurgische Ablatio testis erfolgt ist. Zur Behandlung von Patienten, die auf andere endokrine Therapieformen nicht ansprachen oder für die eine andere endokrine Therapie nicht verträglich, aber notwendigerweise indiziert ist.
Cyproteronacetat G03HA01 Androcur®	Zur palliativen Therapie des metastasierenden oder lokal fortgeschrittenen, inoperablen Prostatakarzinoms, wenn sich die Behandlung mit LHRH-Analoga oder der operative Eingriff als unzureichend erwiesen haben, kontraindiziert sind oder der oralen Therapie der Vorzug gegeben wird. Initial zur Verhinderung von unerwünschten Folgeerscheinungen und Komplikationen, die zu Beginn einer Behandlung mit LHRH-Agonisten durch den anfänglichen Anstieg des Serum -Testosteron hervorgerufen werden können. Zur Behandlung von Hitzewallungen, die unter der Behandlung mit LHRH-Agonisten oder nach Hodenentfernung auftreten.

GnRH-Antagonisten	
Abarelix L02BX01 Plenaxis®[1]	Plenaxis® ist angezeigt zur Einleitung einer hormonalen Kastration bei fortgeschrittenem oder metastasierendem hormonabhängigem Prostatakarzinom, wenn eine Androgensuppression erforderlich ist.
Degarelix L02BX02 FIRMAGON®	FIRMAGON ist ein Gonadotropin-Releasing-Hormon-(GnRH)-Antagonist zur Behandlung von erwachsenen männlichen Patienten mit fortgeschrittenem hormonabhängigen Prostatakarzinom.
GnRH-Agonisten	
Buserelin L02AE01 Profact®	Profact Depot 9,45 mg 3-Monatsimplantat ist angezeigt bei Erwachsenen zur Behandlung des fortgeschrittenen hormonempfindlichen Prostatakarzinoms. Profact Depot 9,45 mg 3-Monatsimplantat ist jedoch nicht angezeigt nach beidseitiger Orchiektomie, da es in diesem Fall zu keiner weiteren Absenkung des Testosteronspiegels kommt.
Goserelin L02AE03 Zoladex®	Behandlung von Patienten mit fortgeschrittenem Prostatakarzinom, bei denen eine endokrine Behandlung angezeigt ist.
Histrelin L02AE05 Vantas®	Palliative Behandlung bei fortgeschrittenem Prostatakrebs.
Leuprorelin L02AE02 Lutrate®	Lutrate® Depot ist indiziert für die palliative Behandlung von lokal fortgeschrittenem oder metastasiertem Prostatakrebs.
Triptorelin L01AA06 Pamorelin®	Pamorelin LA 3,75 mg ist indiziert zur Behandlung des • lokal fortgeschrittenen oder metastasierenden, hormonabhängigen Prostatakarzinoms. • lokal fortgeschrittenen, hormonabhängigen Prostatakarzinoms; begleitend zur und nach der Strahlentherapie.
Zytostatika	
Estramustin L01XX11 Estramustin-Uropharm®	Palliative Behandlung des fortgeschrittenen hormonrefraktären Prostatakarzinoms

[1] Nicht verkehrsfähig

Docetaxel L01CD02 Taxotere®	TAXOTERE ist in Kombination mit Prednison oder Prednisolon zur Behandlung von Patienten mit hormonrefraktärem metastasiertem Prostatakarzinom angezeigt.
Cabazitaxel L01CD04 JEVTANA®	JEVTANA ist in Kombination mit Prednison oder Prednisolon zur Behandlung von erwachsenen Patienten mit metastasiertem kastrationsresistentem Prostatakarzinom angezeigt, die mit einem Docetaxel-basierten Therapieschema vorbehandelt sind.
Mitoxantron L01D B07 Mitoxantron Accord®	Mitoxantron Accord ist in Kombination mit Corticosteroiden indiziert zur Palliation (z.B. Schmerzlinderung) beim fortgeschrittenen kastrationsresistenten Prostatakarzinom.
Neuartige Hormontherapeutika	
Enzalutamid L02BB04 Xtandi®	Xtandi ist angezeigt: • zur Behandlung erwachsener Männer mit metastasiertem kastrationsresistentem Prostatakarzinom mit asymptomatischem oder mild symptomatischem Verlauf nach Versagen der Androgenentzugstherapie, bei denen eine Chemotherapie klinisch noch nicht indiziert ist • zur Behandlung erwachsener Männer mit metastasiertem kastrationsresistentem Prostatakarzinom, deren Erkrankung während oder nach einer Chemotherapie mit Docetaxel fortschreitet.
Abirateronacetat L02BX03 Zytiga®	ZYTIGA ist indiziert mit Prednison oder Prednisolon: • zur Behandlung des neu diagnostizierten Hochrisiko-metastasierten hormonsensitiven Prostatakarzinoms (mHSPC) bei erwachsenen Männern in Kombination mit Androgenentzugstherapie (androgen deprivation therapy, ADT) • zur Behandlung des metastasierten kastrationsresistenten Prostatakarzinoms (mCRPC) bei erwachsenen Männern mit asymptomatischem oder mild symptomatischem Verlauf der Erkrankung nach Versagen der Androgenentzugstherapie, bei denen eine Chemotherapie noch nicht klinisch indiziert • zur Behandlung des mCRPC bei erwachsenen Männern, deren Erkrankung während oder nach einer Docetaxel-haltigen Chemotherapie progredient ist.
Radionuklide	
Strontium-89 V10BX01 Metastron™	Metastron™ wird als Ergänzung oder Alternative zur palliativen Radiotherapie bei der Behandlung von durch Skelettmetastasen des Prostatakarzinoms hervorgerufenen Knochenschmerzen eingesetzt, wenn eine Hormontherapie nicht erfolgreich verlaufen ist.
Samarium-153 V10BX02 Quadramet®	Quadramet® ist zur Linderung von Knochenschmerzen bei Patienten mit multiplen schmerzhaften osteoblastischen Skelettmetastasen indiziert, die in der Knochenszintigraphie Technetium (99mTc)-markierte Bisphosphonate anreichern. Das Vorliegen von osteoblastische Meta-stasen, die Technetium (99mTc)-markierte Bisphosphonate anreichern, sollte vor der Behandlung bestätigt worden sein. (SPC 2012-08)
Rhenium-186 V10AX05	Rheniumsulfid (186Re) wird eingesetzt für die Radiosynoviorthese mittelgroßer Gelenke […] zur Behandlung einer chronischen Synovialitis mit rezidivierenden Gelenkergüssen bei rheumatoider Arthritis, seronegativer Spondylarthropathie (z.B. reaktive Arthritis, Psoriasisarthritis),

Rheniumsulfid (186Re) CIS bio international	pigmentierter villonodulärer Synovitis (nach erfolgter Operation), Hämophilie mit Arthropathie (zur Blutungsprophylaxe). Rheniumsulfid (186Re) darf bei chronisch-entzündlichen Gelenkerkrankungen nur eingesetzt werden, wenn eine vorausgehende 6-monatige konservative Therapie einschließlich intraartikulärer Kortikoidinjektion nicht zum Erfolg geführt hat. […].
Wirkstoffe mit Einfluss auf die Knochenstruktur und die Mineralisation:	
Zoledronsäure M05BA08 generisch	- Prävention skelettbezogener Komplikationen (pathologische Frakturen, Wirbelkompressionen, Bestrahlung oder Operation am Knochen oder tumorinduzierte Hyperkalzämie) bei erwachsenen Patienten mit fortgeschrittenen, auf das Skelett ausgedehnten, Tumorerkrankungen. - Behandlung erwachsener Patienten mit tumorinduzierter Hyperkalzämie (TIH).
Risedronsäure M05BA07 generisch	[…]. Behandlung der Osteoporose bei Männern mit hohem Frakturrisiko.
Ibandronsäure M05BA06 generisch	- Prävention skelettbezogener Ereignisse (pathologische Frakturen, Knochenkomplikationen, die eine Radiotherapie oder einen chirurgischen Eingriff erfordern) bei Patienten mit Brustkrebs und Knochenmetastasen - Behandlung von tumorinduzierter Hyperkalzämie mit oder ohne Metastasen.
Alendronsäuren M05BA04 generisch	[…]. Zur Therapie der Osteoporose bei Männern. […]
Pamidronsäure M05BA03 generisch	Behandlung von Erkrankungen, die mit einer erhöhten Osteoklastenaktivität einhergehen: - Tumorinduzierte Hyperkalzämie - Osteolytische Läsionen bei Patienten mit Brustkrebs-assoziierten Knochenmetastasen […]
Clodronsäuren M05BA02 generisch	Osteolyse infolge von Knochenmetastasen solider Tumoren (z.B. Mamma-, Prostata-, Schilddrüsenkarzinom) oder infolge hämatologischer Neoplasien (z.B. Plasmozytom). Hypercalcämie infolge ausgedehnter Knochenmetastasierung oder durch maligne Tumoren induzierte Knochenzerstörung ohne Knochenmetastasen.
Denosumab M05BX04 Xgeva®, Prolia®	Prävention skelettbezogener Komplikationen (pathologische Fraktur, Bestrahlung des Knochens, Rückenmarkkompression oder operative Eingriffe am Knochen) bei Erwachsenen mit fortgeschrittenen Krebserkrankungen und Knochenbefall (siehe Abschnitt 5.1). (Xgeva®) […]. Behandlung von Knochenschwund im Zusammenhang mit Hormonablation bei Männern mit Prostatakarzinom mit erhöhtem Frakturrisiko. Prolia® vermindert bei Männern mit Prostatakarzinom unter Hormonablationstherapie signifikant das Risiko für vertebrale Frakturen. (Prolia®)
Glucocorticoide:	
Prednison H02AB07 generisch	Palliativtherapie maligner Erkrankungen Hinweis: Prednison kann zur Symptomlinderung, z.B. bei Inappetenz, Anorexie und allgemeiner Schwäche bei fortgeschrittenenmalignen Erkrankungen nach Ausschöpfung spezifischer Therapiemöglichkeiten angewendet werden. Einzelheiten sind der aktuellen Fachliteratur zu entnehmen.
Prednisolon	Palliativtherapie maligner Erkrankungen Hinweis: Prednisolon kann zur Symptomlinderung, z.B. bei Inappetenz, Anorexie und allge-meiner

H02AB06 generisch	Schwäche bei fortgeschrittenen malignen Erkrankungen nach Ausschöpfung spezifischer Therapiemöglichkeiten angewendet werden. Einzelheiten sind der aktuellen Fachliteratur zu entnehmen.
Methylprednisolon H02AB04 generisch	als ergänzende Maßnahme bei einer Zytostatika- oder Strahlentherapie im Rahmen bestehender Schemata zur Kombinationstherapie, palliativen Therapie bzw. antiemetischen Therapie.
Dexamethason H02AB02 generisch	Palliativtherapie maligner Tumoren.

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2018-B-246 (Radium-223-dichlorid)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	28. August 2018

Inhaltsverzeichnis

Abkürzungsverzeichnis

ADT	androgen deprivation therapy
AE	Adverse event
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BSC	Best supportive Care
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
HSPC	Hormone sensitive prostate cancer
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LHRH	luteinizing hormone-releasing hormone
LoE	Level of Evidence
mCRPC	metastatic castration-resistant prostate cancer
mHSPC	Hochrisiko-metastasierten hormonsensitiven Prostatakarzinoms
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
OS	Overall Survival
PCa	prostate cancer
PFS	Progression free survival
PSA	prostate-specific antigen
QoL	quality of life
rPFS	Radiographic progression-free survival
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
SSE	symptomatic skeletal events
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Behandlung von Erwachsenen mit kastrationsresistentem Prostatakarzinom, symptomatischen Knochenmetastasen ohne bekannte viszerale Metastasen

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Prostatakarzinom* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 08.08.2018 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 477 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 28 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 IQWiG Berichte/G-BA Beschlüsse

G-BA, 2012 [10].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichem Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V. Geltende Fassung - Abirateronacetat, Beschluss vom 29. März 2012 (gültig bis: unbefristet)

Anwendungsgebiet

Zytiga® ist indiziert mit Prednison oder Prednisolon zur Behandlung des metastasierten kastrationsresistenten Prostatakarzinoms bei erwachsenen Männern, deren Erkrankung während oder nach einer Docetaxel-haltigen Chemotherapie progredient ist.

Zweckmäßige Vergleichstherapie

Patienten mit metastasiertem kastrationsresistentem Prostatakarzinom, die während oder nach einer Docetaxel-haltigen Chemotherapie progredient sind und für die eine erneute Behandlung mit Docetaxel nicht mehr infrage kommt: Zweckmäßige Vergleichstherapie: Palliative Behandlung mit Dexamethason,Prednison, Prednisolon oder Methylprednisolon sowie "Best Supportive Care" (z.B. adäquate Schmerztherapie).

Als "Best Supportive Care" (BSC) wird die Therapie verstanden, die eine bestmögliche, patientenindividuell optimierte, unterstützende Behandlung zur Linderung von Symptomen und Verbesserung der Lebensqualität gewährleistet.

b) Patienten mit metastasiertem kastrationsresistentem Prostatakarzinom, die nach einer Docetaxel-haltigen Chemotherapie progredient sind, grundsätzlich aber noch für eine adäquate Docetaxel-haltige Chemotherapie infrage kommen: Zweckmäßige Vergleichstherapie: Docetaxel in Kombination mit Prednison oder Prednisolon (Docetaxel-Retherapie).

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Gegenüber BSC: Hinweis auf einen beträchtlichen Zusatznutzen.

Gegenüber Docetaxel-Retherapie: Da die erforderlichen Nachweise nicht vollständig vorgelegt worden sind, gilt der Zusatznutzen im Verhältnis zur zweckmäßigen Vergleichstherapie als nicht belegt (§ 35a Abs. 1 Satz 5 SGB V).

G-BA, 2014 [11].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichem Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V. Geltende Fassung - Abirateronacetat (neues Anwendungsgebiet: Prostatakarzinom, nach Versagen einer Androgenentzugstherapie, vor Chemotherapie), Beschluss vom 04. Juli 2013 (gültig bis: unbefristet)

Anwendungsgebiet

Zytiga® ist zugelassen in Kombination mit Prednison oder Prednisolon:

- zur Behandlung des metastasierten kastrationsresistenten Prostatakarzinoms bei erwachsenen Männern mit asymptomatischem oder mild symptomatischem Verlauf der Erkrankung nach Versagen der Androgenentzugstherapie, bei denen eine Chemotherapie noch nicht klinisch indiziert ist.

Vergleichstherapie

Die zweckmäßige Vergleichstherapie für Abirateronacetat zur Behandlung des metastasierten, kastrationsresistenten Prostatakarzinoms bei erwachsenen Männern, deren Erkrankung nach Versagen einer konventionellen Androgenentzugstherapie asymptomatisch oder mild symptomatisch ist, ist das abwartende Vorgehen unter Beibehaltung der bestehenden konventionellen Androgendeprivation oder gegebenenfalls die kombinierte, maximale Androgenblockade mit einem nichtsteroidalen Antiandrogen (Flutamid, Bicalutamid).

Erläuterungen: Unter konventioneller Androgenentzugstherapie wird im Rahmen des vorliegenden Anwendungsgebietes die operative Kastration oder die medikamentöse Kastration durch Therapie durch LHRH-Analoga oder GnRH-Antagonisten verstanden und unter "Versagen" eine auf der Grundlage von Surrogatparametern (z. B. PSA-Anstieg und radiographischer Progress oder Up-Grading) definierte Krankheitsprogression. Nach Versagen einer konventionellen Androgenentzugstherapie stellt die kombinierte, maximale Androgenblockade mit einem nicht-steroidalen Antiandrogen eine mögliche Therapieoption dar, deren Einsatz jedoch aufgrund der zu erwartenden höheren Nebenwirkungen gegenüber der geringen Überlebensverlängerung sorgfältig mit dem Patienten abzuwägen ist. Bei der Erkrankung des metastasierten, kastrationsresistenten Prostatakarzinoms handelt es sich um eine palliative Therapiesituation. Dem Erhalt der Lebensqualität und der Symptomkontrolle kommen daher besondere Bedeutung zu.

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Hinweis für einen beträchtlichen Zusatznutzen.

G-BA, 2012 [15].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichem Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V. Geltende Fassung - Cabazitaxel, Beschluss vom 29. März 2012 (gültig bis: unbefristet)

Anwendungsgebiet

Jevtana® ist in Kombination mit Prednison oder Prednisolon zur Behandlung von Patienten mit hormonrefraktärem metastasiertem Prostatakarzinom angezeigt, die mit einem Docetaxel-basierten Therapieschema vorbehandelt sind.

Vergleichstherapie

a) Patienten mit hormonrefraktärem metastasiertem Prostatakarzinom, die während oder nach einer Docetaxel-haltigen Chemotherapie progredient sind und für die eine erneute Behandlung mit Docetaxel nicht mehr infrage kommt: Palliative Behandlung mit Dexamethason, Prednison, Prednisolon oder Methylprednisolon sowie "Best Supportive Care" (z.B. adäquate Schmerztherapie).

Als "Best Supportive Care" (BSC) wird die Therapie verstanden, die eine bestmögliche, patientenindividuell optimierte, unterstützende Behandlung zur Linderung von Symptomen und Verbesserung der Lebensqualität gewährleistet.

b) Patienten mit hormonrefraktärem metastasiertem Prostatakarzinom, die nach einer Docetaxel-haltigen Chemotherapie progredient sind, grundsätzlich aber noch für eine adäquate Docetaxel-haltige Chemotherapie infrage kommen: Docetaxel in Kombination mit Prednison oder Prednisolon (Docetaxel-Retherapie).

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Gegenüber „Best Supportive Care“: Hinweis auf einen geringen Zusatznutzen.

Gegenüber Docetaxel-Retherapie: Da die erforderlichen Nachweise nicht vollständig vorgelegt worden sind, gilt der Zusatznutzen im Verhältnis zur zweckmäßigen Vergleichstherapie als nicht belegt (§ 35a Abs. 1 Satz 5 SGB V).

G-BA, 2014 [13].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichem Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V. Geltende Fassung - Radium-223-dichlorid, Beschluss vom 19. Juni 2014 (gültig: unbefristet)

Anwendungsgebiet

zur Behandlung von Erwachsenen mit kastrationsresistentem Prostatakarzinom, symptomatischen Knochenmetastasen ohne bekannte viszerale Metastasen.

Zweckmäßige Vergleichstherapie

Patienten, für die eine Behandlung mit Docetaxel infrage kommt: Docetaxel in Kombination mit Prednison oder Prednisolon.

Patienten, für die eine Behandlung mit Docetaxel nicht infrage kommt: Best-Supportive-Care (insbesondere adäquate Schmerztherapie, Behandlung mit Bisphosphonaten und/oder Radionukliden)

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Patienten, für die eine Behandlung mit Docetaxel infrage kommt: Ein Zusatznutzen ist nicht belegt.

Patienten, für die eine Behandlung mit Docetaxel nicht infrage kommt: Hinweis für einen beträchtlichen Zusatznutzen.

G-BA, 2014 [14].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichem Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V. Geltende Fassung - Enzalutamid, Beschluss vom 20. Februar 2014 (gültig: unbefristet)

Anwendungsgebiet

Enzalutamid (Xtandi®) ist angezeigt zur Behandlung erwachsener Männer mit metastasiertem kastrationsresistentem Prostatakarzinom, deren Erkrankung während oder nach einer Chemotherapie mit Docetaxel fortschreitet.

Vergleichstherapie

Die zweckmäßige Vergleichstherapie für Enzalutamid zur Behandlung des metastasierten, kastrationsresistenten Prostatakarzinoms bei erwachsenen Männern, deren Erkrankung während oder nach einer Chemotherapie mit Docetaxel fortschreitet, ist Best-Supportive-Care (z. B. adäquate Schmerztherapie).

Als Best-Supportive-Care wird die Therapie verstanden, die eine bestmögliche, patientenindividuell optimierte, unterstützende Behandlung zur Linderung von Symptomen und Verbesserung der Lebensqualität gewährleistet.

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Hinweis für einen beträchtlichen Zusatznutzen

G-BA, 2015 [12].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichem Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V. Geltende Fassung - Enzalutamid (neues Anwendungsgebiet), Beschluss vom 18. Juni 2015 (gültig bis: unbefristet)

Anwendungsgebiet

Enzalutamid (Xtandi®) ist angezeigt zur Behandlung erwachsener Männer mit metastasiertem kastrationsresistentem Prostatakarzinom mit asymptomatischem oder mild symptomatischem Verlauf nach Versagen der Androgenentzugstherapie, bei denen eine Chemotherapie klinisch noch nicht indiziert ist.

Vergleichstherapie

Für Enzalutamid zur Behandlung des metastasierten kastrationsresistenten Prostatakarzinoms bei erwachsenen Männern mit asymptomatischem oder mild symptomatischem Verlauf der Erkrankung nach Versagen der Androgenentzugstherapie, bei denen eine Chemotherapie noch nicht klinisch indiziert ist, ist die zweckmäßige Vergleichstherapie:

- Das abwartende Vorgehen unter Beibehaltung der bestehenden konventionellen Androgendeprivation

  oder gegebenenfalls

- die kombinierte, maximale Androgenblockade mit einem nichtsteroidalen Antiandrogen (Flutamid, Bicalutamid)

  oder

- Abirateronacetat unter Beibehaltung der bestehenden Androgendeprivation.

Erläuterung: Unter konventioneller Androgenentzugstherapie wird im Rahmen des vorliegenden Anwendungsgebietes die operative Kastration oder die medikamentöse Kastration durch Therapie durch LHRH-Analoga oder GnRH-Antagonisten verstanden. Bei Krankheitsprogression trotz einer konventionellen Androgenentzugstherapie stellt die kombinierte, maximale Androgenblockade eine mögliche Therapieoption dar, deren Einsatz jedoch aufgrund der zu erwartenden höheren Nebenwirkungen gegenüber der geringen Überlebensverlängerung sorgfältig mit dem Patienten abzuwägen ist. Bei der Erkrankung des metastasierten, kastrationsresistenten Prostatakarzinoms handelt es sich um eine palliative Therapiesituation. Dem Erhalt der Lebensqualität und der Symptomenkontrolle kommen daher besondere Bedeutung zu.

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Gegenüber dem abwartenden Vorgehen unter Beibehaltung der bestehenden konventionellen Androgendeprivation: Hinweis auf einen beträchtlichen Zusatznutzen.

G-BA, 2008 [9].

Protonentherapie, Indikation: Prostatakarzinom. Abschlussbericht des Unterausschusses „Methodenbewertung“ des Gemeinsamen Bundesausschusses; Beschlussdatum: 19.06.2008; Inkrafttreten: 01.01.2009

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Der Gemeinsame Bundesausschuss hat in seiner Sitzung am 19. Juni 2008 beschlossen, die Richtlinie des Gemeinsamen Bundesausschusses zu Untersuchungs- und Behandlungsmethoden im Krankenhaus (Richtlinie Methoden Krankenhausbehandlung) in der Fassung vom 21. März 2006 (BAnz. S. 4466), zuletzt geändert am 18. Oktober 2007 (BAnz. 2008 S. 295), wie folgt zu ändern:

(…) In Anlage II „Methoden, deren Bewertungsverfahren ausgesetzt sind“ der Richtlinie wird folgende Nummer angefügt:

- „2 Protonentherapie
- 2.1 Protonentherapie beim Prostatakarzinom

Beschluss gültig bis 31.12.2018“

3.2 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

3.3 Systematische Reviews

Wang Y et al., 2018 [27].

Effectiveness and tolerability of targeted drugs for the treatment of metastatic castration-resistant prostate cancer: a network meta-analysis of randomized controlled trials

Fragestellung

Network meta-analysis to assess the effectiveness and tolerability of targeted agents for mCRPC.

Methodik

Population:

- patients had mCRPC

Intervention/Komparator:

- targeted agents were used for treatment, and the control group received another type of targeted agents or placebo

Endpunkt:

- Progression-free survival (PFS) and overall survival (OS). The tolerability outcome was severe adverse events (AEs) of grade ≥ 3.

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, and the Cochrane Library through Sep 5, 2017.

Qualitätsbewertung der Studien:

- Cochrane Collaboration tool

Ergebnisse

Anzahl eingeschlossener Studien:

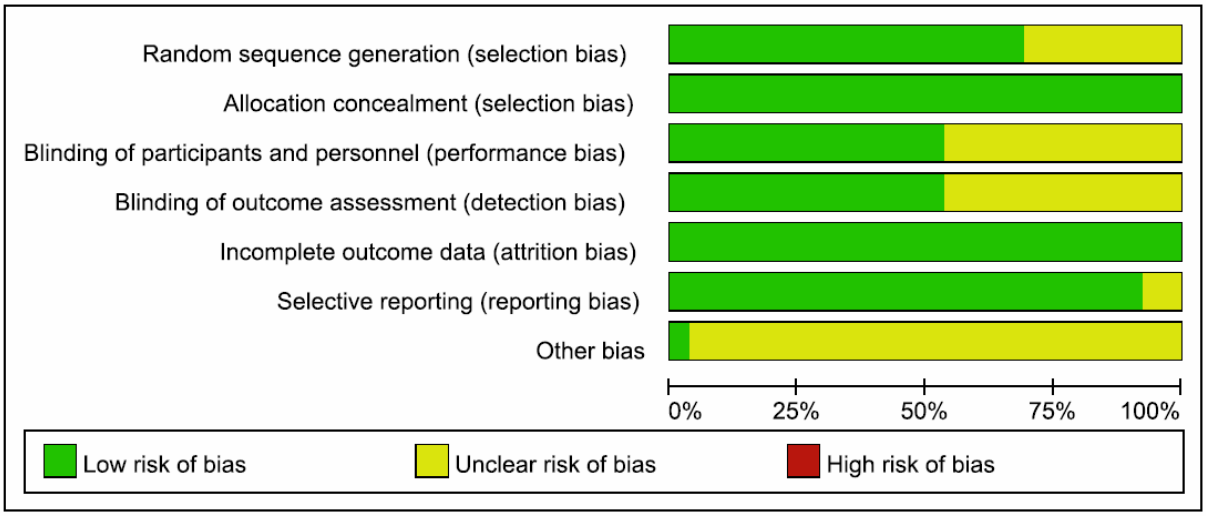
- Twenty-six articles assessing a total of 20,314 patients.

Charakteristika der Population:

- Generally, the included patients were permitted to use prednisone, luteinizing hormone-releasing hormone (LHRH) analogs, and bisphosphonates, among others, if needed, and were provided best supportive care. The follow-up periods were determined from the longest follow-up based on OS.

Qualität der Studien:

- Because all the included studies were RCTs with a blinded design, the overall quality of the included studies was good. However, we cannot ignore the fact that most studies had received funding from pharmaceutical companies.



Studienergebnisse:

- Traditional meta-analysis: Targeted agents stat. significantly prolong PFS in mCRPC patients vs. Placebo irrespective of whether the patients had previously received chemotherapy (I^2 = 94.3%; hazard ratio (HR): 0.74; 95% confidence interval (CI): 0.65-0.84; $p < 0.001$).
- In network analysis, we included 16 targeted agents. All targeted agents were directly compared with placebo except for bicalutamide, which was directly compared with enzalutamide. Other than the placebo, enzalutamide was the most studied agent. In addition, the results of the comparison between aflibercept and placebo were the most accurate. In network comparisons, orteronel (logHR: − 0.35; 95% CI − 0.52, 0.18), ipilimumab (logHR: − 0.38; 95% CI − 0.56, − 0.19), enzalutamide (logHR: − 1.03; 95% CI − 1.20, 0.86), and abiraterone (logHR: 0.55; 95% CI :0.71, :0.39) were superior to placebo. Intetumumab was inferior to placebo (logHR: 0.55; 95% CI 0.07, 1.03).In addition, the surface under the cumulative ranking curve (SUCRA) ranking from the network analysis showed that enzalutamide was the most effective in improving the PFS of mCRPC patients (100%), followed by abiraterone (90.1%) and tasquinimod (84.2%).
- Traditional meta-analysis: Additionally, targeted agents could clearly prolong OS in mCRPC patients vs. Placebo (I^2 = 71.6%; HR: 0.91; 95% CI: 0.85-0.97; $p < 0.001$). However, the difference was not significant in chemotherapy-naïve patients (I^2 = 64.6%). Abiraterone and zibotentan were both investigated in three related studies. In addition, the results of comparison between abiraterone and placebo were the most acurrate.
- In network comparisons, enzalutamide (logHR: − 0.35; 95% CI − 0.50 to − 0.20) and abiraterone (logHR: − 0.27; 95% CI − 0.41 to − 0.13) were superior to placebo, and lenalidomide were inferior to placebo (logHR: 0.43; 95% CI 0.12–0.73). Furthermore, based on SUCRA ranking, enzalutamide was the most effective in improving the OS of mCRPC patients (97.2%), followed by abiraterone (91.1%) and zibotentan (65.8%).

- Intetumumab was associated with the lowest incidence of severe AEs (94.9%), followed by atrasentan (85.1%) and placebo (79.3%).

Subgroup analyses

- Cluster ranking for PFS and severe AEs:
  - Enzalutamide and abiraterone were ideal for improving PFS with a low risk of causing severe AEs. Moreover, bicalutamide, tasquinimod, orteronel, and bevacizumab were moderately effective in improving PFS with acceptable risks of causing severe AEs.
- Cluster ranking for OS and severe AEs:
  - Enzalutamide and abiraterone were still ideal agents; zibotentan, orteronel, and bevacizumab were moderately effective in improving OS with acceptable risks of severe AEs.
  - In patients who had previously received chemotherapy, cluster ranking of PFS and severe AEs showed that enzalutamide was an ideal agent for improving survival and that abiraterone and orteronel could improve PFS with acceptable risks of causing severe AEs.
  - Furthermore, enzalutamide was an ideal agent for improving OS, and abiraterone was moderately effective in improving OS with an acceptable risk of causing severe AEs
- Combination chemotherapy or not:
  - When not combined with chemotherapy, enzalutamide and abiraterone were ideal for improving PFS with a low risk of causing severe AEs.
  - In terms of OS, enzalutamide and abiraterone were still beneficial for improving survival. However, there were no studies that used enzalutamide and abiraterone in combination therapy.
  - Furthermore, bevacizumab, aflibercept, and AT-101 were superior to placebo in improving PFS, albeit with a high risk of causing severe AEs.
  - Dasatinib was moderately effective in improving PFS with a moderate risk causing of severe AEs.
  - Atrasentan and zibotentan were similar in effectiveness to placebo.
  - However, bevacizumab and aflibercept were effective in improving OS with a high risk of causing severe AEs.
  - Zibotentan and dasatinib were moderately beneficial over placebo.

Anmerkung/Fazit der Autoren

In patients with mCRPC, enzalutamide, abiraterone and tasquinimod can prolong PFS, and enzalutamide and abiraterone can prolong OS. Additionally, enzalutamide and abiraterone can improve both PFS and OS with a low risk of causing severe AEs.

Summers N et al., 2017 [24].

Siehe auch: Perletti et al. 2015 [20] & Song et al. 2018 [23]

Efficacy and safety of post-docetaxel therapies in metastatic castration-resistant prostate cancer: a systematic review of the literature.

Fragestellung

to assess published efficacy and safety data for select mCRPC therapies – such as abiraterone, cabazitaxel, and enzalutamide – in the post-docetaxel setting.

Methodik

Population:

- patients aged 18 years and older who had a diagnosis of mCRPC and who were receiving second-line or later treatment with a therapy of interest (cabazitaxel, abiraterone, enzalutamide, radium-223, sipuleucel-T, mitoxantrone, ipilimumab, or estramustine) after previous treatment with a docetaxel- or taxane-based regimen.

Intervention:

- cabazitaxel, abiraterone, enzalutamide, radium-223, sipuleucel-T, mitoxantrone, ipilimumab, or estramustine

Komparator:

- Placebo or active treatment comparator, or no comparator (for non-RCTs only)

Endpunkt:

- survival outcomes, time to progression, response data, skeletal-related events (SREs), prostate-specific antigen (PSA) response, time to PSA progression, time to opiate use, time to pain progression, adverse events (AEs), health-related quality of life

Recherche/Suchzeitraum:

- MEDLINE, Embase, and Cochrane CENTRAL, in conjunction with hand searches of multiple congress abstracts in February 2015.

Qualitätsbewertung der Studien:

- RCTs were assessed using both a qualitative appraisal and a study grade adapted from the University of York's Centre for Reviews and Dissemination systematic review guidance. Non-RCT studies were evaluated using an adaptation of widely cited checklists by Downs and Black for non-economic studies (…)

Ergebnisse

Anzahl eingeschlossener Studien:

- 3 randomized studies and 107 non-randomized studies

Qualität der Studien (Hinweis: Fokus auf RCT Beurteilung, da non-RCTs generell höheres Biasrisiko):

- In general, the larger phase III double-blind trials (COU-AA-301, ALSYMPCA, and AFFIRM) had the highest study quality, while the TROPIC study received a lower quality assessment due to its open-label design.

Studienergebnisse:

→ *Hinweis: Keine Metaanalytische Auswertung!*

Randomized studies

- Overall survival (OS):
  - Significant improvements in median overall survival (OS) outcomes over placebo for abiraterone (15.8 vs. 11.2 months) and enzalutamide (18.4 vs. 13.6 months), and similar significant improvements were noted for cabazitaxel over mitoxantrone (15.1 vs. 12.7 months).
- PFS:
  - Differences in progression-free survival (PFS) were similarly significant, although variance in the criteria for measuring PFS may limit the extent to which these outcomes can be compared between studies.

Non-randomized evidence

- Results from these studies largely reflected the findings in randomized trials.

Safety:

- All studies reported a relatively high proportion of patients experiencing AEs, including several patients experiencing a grade 3 or higher AE and/or discontinuation related to an AE.
- Some treatments appear to have qualitative differences in AE frequency within the RCT setting, though this distinction is less apparent in non-RCT studies and there are no other notable trends indicating specific safety concerns for the assessed treatments.

Furthermore, safety outcomes reported for cabazitaxel, abiraterone, and enzalutamide were comparable to those reported during treatment with docetaxel.

Anmerkung/Fazit der Autoren

Data reporting randomized, head-to-head comparisons of the various post-docetaxel treatment options in patients with mCRPC is limited, although a substantial body of realworld evidence is emerging. Given that multiple therapies are active in this setting, a systematic review of this space adds objectivity and balance that fosters comparability of the currently available data. In general, OS and PFS gains do not appear to differ considerably across the mCRPC agents we have considered – cabazitaxel, abiraterone, and enzalutamide. Furthermore, these improvements in survival outcomes are associated with toxicity for all of the included therapies, and certain hematologic AEs (notably neutropenia) and diarrhea occurred more frequently in the clinical setting for cabazitaxel-treated patients. Importantly, reported findings were consistent between clinical trials and realworld evidence. Analyses of retrospective datasets may further be used to inform treatment choice to optimize patient outcomes.

Zhao Y et al., 2018 [28].

Siehe auch: Fryzek et al. 2018 [7]

Efficacy and safety of different interventions in castration resistant prostate cancer progressing after docetaxel-based chemotherapy: Bayesian network analysis of randomized controlled trials

Fragestellung

to evaluate the clinical efficacy and safety of pharmacological interventions for CRPC patients progressing after docetaxel-based chemotherapy

Methodik

Population:

- CRPC patients after docetaxel failure: Histologically confirmed prostate cancer aged ≥18 years with castrate levels of serum testosterone (<50 ng/dL) were eligible if they had failed previous docetaxel-containing chemotherapy

Intervention:

- Established therapies for management of CRPC patients after docetaxel failure including chemotherapy, immunotherapy, androgen receptor targeting etc.

Komparator:

- another active agent, Prednisone plus placebo, placebo, or no intervention

Endpunkt:

- OS, PFS, PSA response and adverse events

Recherche/Suchzeitraum:

- PubMed, Web of Science and Embase were searched until Jan 2017.

Qualitätsbewertung der Studien:

- Cochrane Collaboration's Risk of Bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 17 Randomized Controlled Trials (RCTs) comprising 14 different interventions with 12347 patients

Qualität der Studien:

- In fact, none of the trials were thought to have a high risk of bias for any of the methodological quality items assessed.

Studienergebnisse:

- NMA:
  - Compared with control arms, Abiraterone Acetate (HR: 0.70, 95%CrI: 0.63-0.79), Cabazitaxel (HR: 0.70, 95%CrI: 0.51-0.95) and Enzalutamide (HR: 0.63, 95%CrI: 0.53-0.75) presented similar benefits in term of OS.
  - Enzalutamide showed superiority over PFS and PSA response with a highest probability to rank 1, followed by Cabozantinib and Abiraterone Acetate.
  - Moreover, sensitivity analysis showed that Abiraterone Acetate (HR: 0.71, 95%CrI: 0.63-0.78) exhibited the most efficacious intervention of being rank 1 in term of OS compared with control arms, followed by Cabazitaxel and Cetuximab.

- Abiraterone Acetate (OR: 0.86, 95%CrI: 0.35-2.03) and Enzalutamide (OR: 1.22, 95%CrI: 0.31-5.60) presented no significant toxicities compared with control arms, whereas Mitoxantrone, Cabazitaxel, Ixabepilone, Cetuximab, Siltuximab and Rilotumumab were not as well tolerated compared with control arms for adverse events (grade 3-4).

- Pairwise meta-analysis comparison
  - consistent with that of network meta-analysis: Pooled data showed that Abiraterone Acetate (HR: 0.70, 95%CI: 0.62-0.77), Enzalutamide (HR: 0.63, 95%CI: 0.52-0.74), Cabazitaxel (HR: 0.71, 95%CI: 0.63-0.79) presented benefits compared with control in term of OS.
  - Abiraterone Acetate, Enzalutamide, Cabazitaxel and Orteronel were associated with longer PFS and higher PSA response than control arms.

Anmerkung/Fazit der Autoren

In conclusion, our network meta-analysis demonstrated that Abiraterone Acetate, Cabazitaxel and Enzalutamide were associated with favorable OS when compared with control arms. Abiraterone Acetate appears to be efficacious treatment option for mCRPC patients after docetaxel failure because of the higher efficacy and lower adverse events. Similar observations were also noted for PFS and PSA response. Further sensitivity analysis indicated Abiraterone Acetate showed significant benefit in prolonging survival. Future well-designed RCTs and systematic reviews are awaited to confirm the findings of this study.

Magnan S et al., 2015 [17].

Intermittent vs Continuous Androgen Deprivation Therapy for Prostate Cancer A Systematic Review and Meta-analysis

Fragestellung

to conduct a systematic review and meta-analysis comparing the efficacy and tolerability of intermittent vs continuous androgen deprivation therapy in patients with prostate cancer.

Methodik

Population:

- patients with prostate cancer

Intervention/Komparator:

- intermittent vs continuous androgen deprivation therapy

Endpunkt:

- Primary outcomes: overall survival and quality of life. Secondary outcomes: cancer-specific survival, progression-free survival, time to castration resistance, skeletal-related events, and adverse effects

Recherche/Suchzeitraum:

- Cochrane CENTRAL, Medline, Embase,Web of Science, Biosis, National Technical Information Service, OpenSIGLE, and Google Scholar from inception of each database through March 2014

Qualitätsbewertung der Studien:

- Cochrane Collaboration's Risk of Bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 15 trials (6856 patients)

Qualität der Studien:

- All but 1 study had an unclear or high risk of bias

Studienergebnisse:

- No significant difference between intermittent and continuous therapy for overall survival (8 trials, 5352 patients), cancer-specific survival (5 trials, 3613 patients), and progression-free survival (4 trials, 1774 patients).
  - A subgroup analysis of metastatic castration-resistant prostate cancer vs hormone-sensitive prostate cancer was also performed a posteriori. This analysis did not affect the study results!

    → Hinweis: Es wurden keine weiteren Subgruppenergebnisse/analysen berichtet!
- There was minimal difference in patients' self-reported quality of life between the 2 interventions. Most trials observed an improvement in physical and sexual functioning with intermittent therapy.

Anmerkung/Fazit der Autoren

In our systematic review, we observed that intermittent androgen deprivation for the treatment of prostate cancer is not inferior to continuous therapy with respect to overall survival. No major difference in quality of life was observed between groups, although some criteria seemed improved in the intermittent groups in relation with physical and sexual functioning. Intermittent androgen deprivation can be considered as an alternative therapeutic option in patients with prostate cancer. However, the high risk of bias observed in some trials, the unclear optimal approach to the duration of treatment and off-treatment periods and criteria on which it should be based, and the unknown magnitude of effect according to the disease stage warrant further research before it becomes the mandatory standard of care.

Shameem R et al., 2015 [22].

Comparative analysis of the effectiveness of abiraterone before and after docetaxel in patients with metastatic castration-resistant prostate cancer

Fragestellung

to study the efficacy and safety of abiraterone in patients with and without prior chemotherapy.

Methodik

Population:

- Metastatic castration-resistant prostate cancer (CRPC) patients

Intervention:

- abiraterone plus prednisone

Komparator:

- to placebo plus prednisone

Endpunkt:

- OS, PFS, PSA, rPFS, adverse events

Recherche/Suchzeitraum:

- up to April 2014

Qualitätsbewertung der Studien:

- Jadad Score

Ergebnisse

Anzahl eingeschlossener Studien:

- Two phase III RCTs were included (total of 2283 patients)

Charakteristika der Studien:

- A total of 1343 (58.3%) patients received the approved United States Food and Drug Administration abiraterone oral dose of 1 g daily with 5 mg of prednisone twice daily by mouth. Finally, 546 patients in the pre-chemotherapy and 797 in the post-chemotherapy arms were included in the meta-analysis.
- In the post-chemotherapy trial, 70% in the abiraterone arm and 69% in the control arm received one previous cytotoxic chemotherapy regimen and approximately 30% in the abiraterone arm and 31% in the control arm received two distinct previous regimens. All included patients received at least one previous cytotoxic chemotherapy regimen containing docetaxel: docetaxel after a treatment break, single therapy with docetaxel, or docetaxel in combination with other agents.

Qualität der Studien:

- The COU-AA-301 study was given the highest Jadad score of 5, while COU-AA-302 was given a score of 4, based on the 7-item scale

Studienergebnisse:

- Prior chemotherapy did not significantly alter the effect of abiraterone on overall survival and prostate specific antigen (PSA) progression-free survival, but reduced its effect on radiographic-progression-free survival ($P = 0.04$), objective response rate ($P < 0.001$), and PSA response rate ($P < 0.001$).
- Prior chemotherapy significantly increased the specific risk of fluid retention and edema ($P < 0.001$) and hypokalemia ($P < 0.001$), but decreased the risk of all-grade hypertension ($P < 0.001$) attributable to abiraterone.
- There was no significant difference of cardiac disorders associated with abiraterone between the two settings ($P= 0.58$).

Anmerkung/Fazit der Autoren

In conclusion, our meta-analysis of RCTs has demonstrated that abiraterone is associated with a significantly improved radiographic-PFS, objective response rate, PSA response rate in the pre-chemotherapy setting when compared to the post-chemotherapy setting in patients with metastatic CRPC. This emphasizes that these patients may obtain the greatest clinical benefit with early treatment of androgen synthesis inhibition with abiraterone. Further studies may be necessary to determine the effectiveness of abiraterone in the pre-chemotherapy setting in comparison with other new agents including the androgen signaling pathway inhibitor enzalutamide or vaccines.

Tunio M et al., 2015 [25].

Comparative efficacy, tolerability, and survival outcomes of various radiopharmaceuticals in castration-resistant prostate cancer with bone metastasis: a meta-analysis of randomized controlled trials

Fragestellung

to assess the impact of radiopharmaceuticals (RPs) in castration-resistant prostate cancer (CRPC) on pain control, symptomatic skeletal events (SSEs), toxicity profile, quality of life (QoL), and overall survival (OS).

Methodik

Population:

- CRPC patients with confirmed bone metastasis

Intervention/Komparator:

- Radiopharmaceuticals (siehe Ergebnisteil)

Endpunkt:

- reductions in pain intensity and SSE, functional mobility and QoL, OS, and toxicity profile

Recherche/Suchzeitraum:

- PubMed/MEDLINE, CANCERLIT, EMBASE, Cochrane Library database, and other search engines were searched. *Hinweis*: Kein Suchzeitraum angegeben.

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- Eight RCTs with a total patient population of 1,877 patients

Charakteristika der Population:

- All RCTs included metastatic CRPC patients with bone metastasis

Qualität der Studien:

- Four RCTs (50%) were rated to be in “high risk” of bias, two trials (25%) were considered to be in “low risk”, and two trials (25%) were classified as “unclear” with respect to the risk of bias

Studienergebnisse:

- The use of RP was associated with significant reduction in pain intensity and SSE (OR: 0.63, 95% CI: 0.51–0.78, I_2=27%, *P*,0.0001), improved QoL (OR: 0.71, 95% CI: 0.55–0.91, I_2=65%, three trials, 1,178 patients, *P*=0.006), and a minimal improved OS (OR: 0.84, 95% CI: 0.64–1.04, I_2=47%, seven trials, 1,845 patients, *P*=0.11).
- A subgroup analysis suggested an improved OS with radium-223 (OR: 0.68, 95% CI: 0.51–0.90, one trial, 921 patients) and strontium-89 (OR: 0.21, 95% CI: 0.05–0.91, one trial, 49 patients).
- Strontium-89 (five trials) was associated with increased rates of grade 3 and 4 thrombocytopenia (OR: 4.26, 95% CI: 2.22–8.18, *P*=0.01), leucopenia (OR: 7.98, 95% CI: 1.82–34.95, *P*=0.02), pain flare (OR: 6.82, 95% CI: 3.42–13.55, *P*=0.04), and emesis (OR: 3.61, 95% CI: 1.76–7.40, *P*=0.02).

Anmerkung/Fazit der Autoren

The use of RPs was associated with significant reduction in SSEs and improved QoL, while the radium-223-related OS benefit warrants further large, RCTs in docetaxel naïve metastatic CRPC patients.

Poorthuis MHF et al., 2017 [21].

First-line non-cytotoxic therapy in chemotherapy naive patients with metastatic castration-resistant prostate cancer: a systematic review of 10 randomised clinical trials

Fragestellung

to systematically evaluate all available treatment options in chemotherapy-naive patients with metastatic castration-resistant prostate cancer (mCRPC)

Methodik

Population:

- chemotherapy-naïve patients with mCRPC

Intervention:

- first-line treatment, including abiraterone, enzalutamide, 223radium, sipuleucel-T, orteronel, or classic androgen receptor-blocker therapy

Komparator:

- placebo, prednisone, or each other

Endpunkt:

- PFS, OS, QoL, AEs

Recherche/Suchzeitraum:

- PubMed, EMBASE, and the Cochrane libraries up to 1 March 2016

Qualitätsbewertung der Studien:

- Cochrane Collaboration's tool and graded the evidence with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group's approach

Ergebnisse

Anzahl eingeschlossener Studien:

- 10 unique RCTs describing seven different comparisons

Qualität der Studien:

- Siehe Ergebnisteil

Studienergebnisse:

- In one RCT, a prolonged OS and PFS (high quality) were found with abiraterone and prednisone compared to placebo plus prednisone.

Table 3 Summary of findings for the comparison: Abiraterone plus prednisone vs placebo plus prednisone.

Patient or population: Chemotherapy-naive asymptomatic or mildly symptomatic patients with mCRPC and without visceral metastases Intervention: Abiraterone plus prednisone Comparison: Placebo plus prednisone						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk Placebo plus prednisone	**Corresponding risk Abiraterone plus prednisone**				
PFS	**649 per 1000**	**420 per 1000** (376–472)	**HR 0.52** (0.45–0.61)	1088 (1 study)	⊕⊕⊕⊕ **high**	
OS Deaths	**714 per 1000**	**637 per 1000** (584–688)	**HR 0.81** (0.70–0.93)	1088 (1 study)	⊕⊕⊕⊕ **high**	
QoL FACT-P deterioration after 1 year	**795 per 1000**	**652 per 1000** (604–700)	**RR 0.82** (0.76–0.88)	1088 (1 study)	⊕⊕⊕⊕ **high**	
Toxicity AE grade ≥3	**437 per 1000**	**533 per 1000** (472–607)	**RR 1.22** (1.08–1.39)	1082 (1 study)	⊕⊕⊕⊕ **high**	

*The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.

- In one RCT, a prolonged OS and PFS (high quality) were found with enzalutamide compared to placebo.

Table 4 Summary of findings for the comparison: Enzalutamide vs placebo.

Patient or population: Chemotherapy-naïve asymptomatic or mildly symptomatic patients with mCRPC Intervention: Enzalutamide Comparison: Placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk Placebo	**Corresponding risk Enzalutamide**				
PFS at 12 months	**191 per 1000**	**39 per 1000** (31–48)	**HR 0.19** (0.15–0.23)	1633 (1 study)	⊕⊕⊕⊕ **high**	
OS at 12 months Survival	**830 per 1000**	**715 per 1000** (654–774)	**HR 0.71** (0.60–0.84)	1717 (1 study)	⊕⊕⊕⊕ **high**	
QoL FACT-P	**229 per 1000**	**396 per 1000** (339–461)	**RR 1.73** (1.48–2.01)	1616 (1 study)	⊕⊕⊕⊕ **high**	
QoL EQ-5D	**159 per 1000**	**277 per 1000** (222–342)	**RR 1.74** (1.40–2.15)	1435 (1 study)	⊕⊕⊕⊕ **high**	
Toxicity AE grade≥ 3	**371 per 1000**	**430 per 1000** (382–482)	**RR 1.16** (1.03–1.30)	1715 (1 study)	⊕⊕⊕⊕ **high**	

The **corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.*

- In two RCTs, a prolonged OS (high and moderate quality) was found with 223radium compared to placebo, but its effect on PFS is unknown.

Table 5 Summary of findings for the comparison: ^{223}Radium vs placebo.

Patient or population: Patients with mCRPC and ≥2 bone metastases and no known visceral metastases. This RCT included patients with previous docetaxel use and docetaxel-naive patients considered unfit for docetaxel Intervention: ^{223}Radium Comparison: Placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk Placebo	**Corresponding risk 223-Radium**				
PFS	–	–	–		–	No evidence available
OS (continuous)	**16.1 months**	**11.5 months**	**HR 0.69** (0.52–0.92)	474 (1 study)	⊕⊕⊕⊕ **high**	Not possible to calculate the mean difference since no details on statistical variability were provided.
OS at 24 months	**129 per 1000**	**64 per 1000** (35–114)	**HR 0.48** (0.26–0.88)	64 (1 study)	⊕⊕⊕⊖ **moderate**†	
QoL meaningful improvement at week 24 by FACT-P total score	**83 per 1000**	**182 per 1000** (96–343)	**RR 2.18** (1.15–4.12)	434 (1 study)	⊕⊕⊕⊕ **high**	
QoL meaningful improvement at week 24 by EQ-5D utility score	**153 per 1000**	**218 per 1000** (139–344)	**RR 1.43** (0.91–2.25)	474 (1 study)	⊕⊕⊕⊖ **moderate**‡	
Toxicity	**592 per 1000**	**575 per 1000** (480–687)	**RR 0.97** (0.81–1.16)	383 (1 study)	⊕⊕⊕⊖ **moderate**‡	
Toxicity Haematological AE grade 3–4	**65 per 1000**	**83 per 1000** (15–467)	**RR 1.29** (0.23–7.24)	64 (1 study)	⊕⊕⊖⊖ **low**†,‡	
Serious AEs	**452 per 1000**	**235 per 1000** (113–479)	**RR 0.52** (0.25–1.06)	64 (1 study)	⊕⊕⊖⊖ **low**†,‡	

The **corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. †High risk of bias because of no blinding of patients and personnel after 12 months with 24 months of follow-up. ‡Lower interval of the CI results in different conclusion than the upper limit.*

- In three RCTs, a prolonged OS (moderate quality) was found with sipuleucel-T compared to placebo, but no prolonged PFS (low quality).

Table 6 Summary of findings for the comparison: Sipuleucel-T vs placebo.

Patient or population: Asymptomatic or mildly symptomatic patients with mCRPC and without visceral metastases Intervention: Sipuleucel-T Comparison: Placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk Placebo	**Corresponding risk Sipuleucel-T**				
PFS	Unknown	Unknown	**IMPACT**: HR 0.95 (0.77–1.17) **D9901 and D9902A**: HR 1.26 (0.95–1.68)	3 studies	⊕⊕⊖⊖ **low**†‡	Continuous outcomes are not provided in the studies and HRs of the two studies could not be pooled, because in the IMPACT study, the risk estimate was defined as the risk in patients treated with sipuleucel-T divided by the risk in patients treated with placebo and in the D9901 and D9902A studies, the risk estimate was defined as the risk in patients treated with placebo divided by the risk in patients treated with sipuleucel-T.
OS	Unknown	Unknown	**IMPACT**: HR 0.78 (0.61–0.98) **D9901 and D9902A**: HR 1.50 (1.10–2.05)	3 studies	⊕⊕⊕⊖ **moderate**†	Continuous outcomes are not provided in the studies and HRs of the two studies could not be pooled, because in the IMPACT study, the risk estimate was defined as the risk in patients treated with sipuleucel-T divided by the risk in patients treated with placebo and in the D9901 and D9902A studies, the risk estimate was defined as the risk in patients treated with placebo divided by the risk in patients treated with sipuleucel-T.
QoL	–	–	–	–	–	No evidence available
Toxicity AE grade 3 or 4 AEs	**340 per 1000**	**320 per 1000** (259 to 402)	**RR 0.94** (0.76–1.18)	720 (3 studies)	⊕⊕⊖⊖ **low**†‡	

The **corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. †IMPACT: unclear risk of bias due to no description of allocation concealment. D9901 and D9902A: unclear risk of bias due to no description of randomisation methods, allocation concealment, blinding methods, and protocol. ‡Lower interval of the CI results in different conclusion than the upper limit.*

- In one RCT a prolonged PFS (high quality) was found with orteronel compared to placebo, but no prolonged OS (moderate quality).

Table 7 Summary of findings for the comparison: Orteronel plus prednisone vs placebo plus prednisone.

Patient or population: Chemotherapy-naive patients with mCRPC and radiographic nodal, bone or visceral metastases Intervention: Orteronel plus prednisone Comparison: Placebo plus prednisone						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk Placebo	**Corresponding risk Orteronel**				
PFS	Unknown	Unknown	**HR 0.71** (0.63–0.80)	1554 (1 study)	⊕⊕⊕⊕ **high**	Continuous outcomes are not provided in the studies
OS	Unknown	Unknown	**HR 0.92** (0.79–1.08)	1554 (1 study)	⊕⊕⊕⊖ **moderate**†	Continuous outcomes are not provided in the studies
QoL	–	–	–	–	–	No evidence available
Toxicity AE grade 3–5	**406 per 1000**	**593 per 1000** (537–659)	**RR 1.46** (1.32–1.62)	1554 (1 study)	⊕⊕⊕⊕ **high**	

The **corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). †Lower interval of the CI results in different conclusion than the upper limit. GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.*

- In one RCT, a prolonged OS (moderate quality) was found with bicalutamide compared to placebo, but its effect on PFS is unknown.

Table 8 Summary of Findings for the comparison: Bicalutamide vs placebo.

Patient or population: Chemotherapy-naive patients with mCRPC Intervention: Bicalutamide Comparison: Placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk Placebo	**Corresponding risk Bicalutamide**				
PFS	–	–	–	–	–	No evidence available
OS	N/A	N/A	**HR 0.78** (0.60–0.99)	203 (1 study)	⊕⊕⊕⊖ **moderate**†	Continuous outcomes are not provided in the studies
QoL		The mean QoL in the intervention groups was **3.19 higher** (1.82–8.20 higher)		203 (1 study)	⊕⊕⊖⊖ **low**†	
Toxicity	–	–	–	0	–	No evidence available

The **corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. †Unclear risk of bias because of details lacking regarding randomisation, allocation concealment, blinding, and a protocol.*

- In one RCT, a prolonged PFS (high quality) was found with enzalutamide compared to bicalutamide, but its effect on OS is unknown.

Table 9 Summary of findings for the comparison: Enzalutamide vs bicalutamide.

Patient or population: Asymptomatic or mildly symptomatic patients with mCRPC and at least two bone lesions or soft tissue metastases Intervention: Enzalutamide Comparison: Bicalutamide						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk Bicalutamide	**Corresponding risk Enzalutamide**				
PFS	Unknown	Unknown	**HR 0.44** (0.34–0.57)	203 (1 study)	⊕⊕⊕⊕ **high**	Continuous outcomes are not provided in the studies
OS	–	–	–	–	–	No evidence available
QoL	–	–	–	0	–	No evidence available
Toxicity AE grade 3–5	**381 per 1000**	**400 per 1000** (309–514)	**RR 1.05** (0.81–1.35)	372 (1 study)	⊕⊕⊕⊖ **moderate**†	

The **corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). CI, confidence interval; RR, risk ratio; HR, hazard ratio. GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. †Lower interval of the CI results in different conclusion than the upper limit.*

Anmerkung/Fazit der Autoren

The best evidence was found for abiraterone and enzalutamide for effective prolongation of OS and PFS to treat chemotherapy-naive patients with mCRPC. However, taking both QoL and AEs into consideration, other treatment modalities could be considered for individual patients.

Iacovelli R et al., 2018 [16].

The Cardiovascular Toxicity of Abiraterone and Enzalutamide in Prostate Cancer

Fragestellung

to update our previous findings related to abiraterone and enzalutamide, including the new available evidence, both in castration-resistant and hormone-sensitive prostate cancer.

Methodik

Population:

- Patients with PC

Intervention:

- abiraterone and enzalutamide +/- prednisone

Komparator:

- placebo +/- prednisone group

Endpunkt:

- all-grade (grades 1-4) and highgrade (grades 3-5) events
  - o A subgroup analysis was performed to highlight any differences in terms of the incidence and RR of cardiovascular toxicity between abiraterone and enzalutamide, and in patients treated with abiraterone

Recherche/Suchzeitraum:

- from 2013 to June 15, 2017

Qualitätsbewertung der Studien:

- Jadad 5-item scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 7 studies covering a total of 8660 patients
- Four studies compared abiraterone plus prednisone over a placebo plus prednisone, whereas the remaining 3 compared enzalutamide over a placebo in 2 studies and enzalutamide over bicalutamide in the last study. Five studies were performed in patients with metastatic CRPC and 2 in patients with metastatic HSPC.

Qualität der Studien:

- One trial has 3 points in the Jadad score, whereas all other studies have 5 points. The median value of 4.7 points confirms the good quality of studies included in the analysis.

Studienergebnisse:

- The use of new hormonal agents was associated with an increased risk of all-grade (RR, 1.36; 95% CI, 1.13-1.64; P = .001) and high-grade (RR, 1.84; 95% CI, 1.21-2.80; P = .004) cardiac toxicity.
- The use of new hormonal agents was also associated with an increased risk of all-grade (RR, 1.98; 95% CI, 1.62-2.43; P = .001) and high-grade (RR, 2.26; 95% CI, 1.84-2.77; P = .004) hypertension compared with the controls.
- Abiraterone was found to significantly increase the risk of both cardiac toxicity and hypertension, whereas enzalutamide significantly increases only the risk of hypertension.
- No differences were found based on the dose of prednisone used with abiraterone.
- HSPC vs. CRPC:

- When studies performed in patients with HSPC were compared with those performed in patients with CRPC, patients treated with abiraterone with CRPC have significant major incidence of highgrade **cardiac toxicity** events compared with patients with HSPC, but no increase of all-grades cardiac toxicity was found. The same evidence was found for patients treated with placebo.
- When studies performed in patients with HSPC were compared with those performed in patients with CRPC, patients treated with abiraterone for HSPC have major incidence of **hypertension**, but the difference was not significant. When the incidence of hypertension was compared in patients treated with placebo, patients with HSPC have a significantly increased incidence of adverse events compared with patients with CRPC.

Anmerkung/Fazit der Autoren

Abiraterone and enzalutamide significantly increase the incidence and RR of cardiovascular toxicity in patients affected by metastatic prostate cancer. Follow-up for the onset of treatment-related cardiovascular events should therefore be considered in these patients.

3.4 Leitlinien

Deutsche Gesellschaft für Urologie (DGU), 2018 [6].

Interdisziplinäre Leitlinie der Qualität S3 zur Früherkennung, Diagnose und Therapie der verschiedenen Stadien des Prostatakarzinoms; Langfassung, Version 5.0

Zielsetzung

Die interdisziplinäre Leitlinie der Qualität S3 zur Früherkennung, Diagnose und Therapie der verschiedenen Stadien des Prostatakarzinoms ist ein evidenz- und konsensbasiertes Instrument, um Früherkennung, Diagnostik und Therapie des Prostatakarzinoms zu verbessern.

Methodik

Grundlage der Leitlinie

- Aktualisierung der LL
- Interdisziplinäre LL-Entwickungsgruppe
- CoI dargelegt und Umgang beschrieben
- Strukturierte Konsensfindung
- Die Leitlinie ist bis zur nächsten Aktualisierung gültig. Vorgesehen sind weitere modulare Aktualisierungen in einem etwa 2-3 jährlichen Abstand

Aktualität der Empfehlungen

- In den Kopfzeilen der Empfehlungen und Statements wurde vermerkt, wann diese erstellt bzw. aktualisiert wurden und ob sie modifiziert oder neu erstellt wurden. Folgende Kategorien der Kennzeichnung werden verwendet:
- *geprüft 2018* = Die Empfehlung bzw. das Statement wurde bei der Erstellung der Leitlinie oder bei einer der anschließenden Aktualisierungen (2011, 2014, 2016) erstellt oder modifiziert. Die Gültigkeit der Empfehlung bzw. des Statements wurde während der Aktualisierung 2018 geprüft und mittels Abstimmung erneut konsentiert.
- *spezifiziert 2018* = Die Empfehlung bzw. das Statement wurde während der Aktualisierung 2018 in Detailaspekten angepasst, die Aussage jedoch nicht verändert.
- *modifiziert 2018* = Die Empfehlung bzw. das Statement wurde während der Aktualisierung 2018 in Teilen oder gänzlich aufgrund neuer Evidenz geändert.
- *neu 2018* = Die Empfehlung bzw. das Statement wurde während der Aktualisierung 2018 neu erstellt.

LoE/GoR

Tabelle 2: Schema der Evidenzgraduierung nach SIGN

Grad	Beschreibung
1++	Qualitativ hochwertige Metaanalysen, systematische Übersichten von RCTs, oder RCTs mit sehr geringem Risiko systematischer Fehler (Bias)
1+	Gut durchgeführte Metaanalysen, Systematische Übersichten von RCTs, oder RCTs mit geringem Risiko systematischer Fehler (Bias)
1-	Metaanalysen, Systematische Übersichten von RCTs, oder RCTs mit hohem Risiko systematischer Fehler (Bias)
2++	Qualitativ hochwertige systematische Übersichten von Fall-Kontroll- oder Kohortenstudien oder qualitativ hochwertige Fall-Kontroll- oder Kohortenstudien mit sehr niedrigem Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und hoher Wahrscheinlichkeit, dass die Beziehung ursächlich ist
2+	Gut durchgeführte Fall-Kontroll-Studien oder Kohortenstudien mit niedrigem Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und moderater Wahrscheinlichkeit, dass die Beziehung ursächlich ist
2-	Fall-Kontroll-Studien oder Kohortenstudien mit einem hohen Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und signifikantem Risiko, dass die Beziehung nicht ursächlich ist
3	Nicht-analytische Studien, z. B. Fallberichte, Fallserien
4	Expertenmeinung

Tabelle 3: Schema der Empfehlungsgraduierung

Empfehlungsgrad	Beschreibung	Ausdrucksweise
A	Starke Empfehlung	soll
B	Empfehlung	sollte
0	Empfehlung offen	kann

Therapie des androgenunabhängigen oder kastrationsresistenten Prostatakarzinoms

6.23	Evidenzbasierte Empfehlung	geprüft 2018
Empfehlungsgrad A	Patienten mit kastrationsresistentem Prostatakarzinom sollen über folgende Inhalte aufgeklärt werden: • Eine Heilung kann nicht erreicht werden. • Für die weitere Behandlung stehen verschiedene Optionen zur Verfügung.	
Level of Evidence 4	Expertenkonsens	
	Gesamtabstimmung: 100 %	

6.24	Evidenzbasierte Empfehlung	geprüft 2018
Empfehlungsgrad B	Bei Patienten mit symptomatischer progredienter Erkrankung unter medikamentöser Kastration sollten die therapeutischen Optionen und das therapeutische Vorgehen interdisziplinär beraten und festgelegt werden.	
Level of Evidence 4	Expertenkonsens	
	Gesamtabstimmung: 97 %	

6.25	Evidenzbasierte Empfehlung	geprüft 2018
Empfehlungsgrad A	Folgende für eine Therapieentscheidung ausschlaggebende Faktoren sollen bedacht werden: • Symptomatik • Nebenwirkungen der Therapieoptionen • Patientenpräferenz • Komorbidität, Lebenserwartung und Lebensqualität • Progressionsdynamik • Lokalisation von Metastasen und generelle Tumorlast.	
Level of Evidence 4	Expertenkonsens	
	Gesamtabstimmung: 100 %	

6.26	Evidenzbasiertes Statement	geprüft 2018
Level of Evidence 4	Behandlungsfähigkeit für Chemotherapie ist keine eindeutig definierte Variable. Es fehlen daher Grenzwerte, ab denen Behandlungsfähigkeit gegeben bzw. nicht gegeben ist.	
	Expertenkonsens	
	Gesamtabstimmung: 97 %	

Erstlinientherapie symptomatische Patienten

6.34	Evidenzbasierte Empfehlung	modifiziert 2018
Empfehlungsgrad A	Patienten mit metastasierter, kastrationsresistenter, symptomatischer progredienter Erkrankung und gutem Allgemeinzustand soll als Erstlinientherapie eine systemische Therapie, bei Bedarf in Kombination mit symptombezogener und supportiver Therapie, angeboten werden. Zur Differenzialtherapie siehe Empfehlungen 6.35, 6.36, 6.37.	
Level of Evidence 1+	Literatur: [764-766; 792].	
	Gesamtabstimmung: 98 %	

6.35	Evidenzbasierte Empfehlung	spezifiziert 2018
Empfehlungsgrad 0	Patienten mit metastasierter, kastrationsresistenter, symptomatischer und progredienter Erkrankung kann Docetaxel als Erstlinientherapie in zwei- oder drei-wöchigen Dosierungsschemata angeboten werden.	
Level of Evidence 1+	Literatur: [764; 765]	
	Gesamtabstimmung: 95 %	

6.36	Evidenzbasierte Empfehlung	modifiziert 2018
Empfehlungsgrad 0	Patienten mit metastasierter, kastrationsresistenter, symptomatischer und progredienter Erkrankung kann (alphabetische Reihenfolge) · Abirateron (in Kombination mit Prednison / Prednisolon) oder · Enzalutamid als Erstlinientherapie angeboten werden.	
A	Patienten sollen darüber aufgeklärt werden, dass in der Zulassungsstudie nur Patienten mit gering symptomatischer Erkrankung behandelt wurden.	
Level of Evidence 1+	Literatur: [766; 768]	
	Gesamtabstimmung: 95 %	

6.37	Evidenzbasierte Empfehlung	spezifiziert 2018
Empfehlungsgrad 0	Patienten mit kastrationsresistenter, symptomatischer, progredienter Erkrankung mit ossären Metastasen ohne Nachweis extra-ossärer, distanter Metastasen kann Radium-223 als Erstlinientherapie angeboten werden.	
Level of Evidence 1+	Literatur: [792]	
	Gesamtabstimmung: 82 %	

6.38	Evidenzbasierte Empfehlung	geprüft 2018
Empfehlungsgrad A	Patienten mit kastrationsresistenter, symptomatischer, progredienter Erkrankung und reduziertem Allgemeinzustand (ECOG ≥ 2, Karnofsky-Index < 70) soll eine symptombezogene Therapie angeboten werden.	
Level of Evidence 4	Expertenkonsens	
	Gesamtabstimmung: 95 %	

6.39	Evidenzbasierte Empfehlung	modifiziert 2018
Empfehlungsgrad 0	Patienten mit kastrationsresistenter, progredienter Erkrankung und reduziertem Allgemeinzustand (ECOG ≥ 2, Karnofsky-Index < 70) kann als Erstlinientherapie zusätzlich eine der folgenden Therapieoptionen angeboten werden: (alphabetische Reihenfolge) • Abirateron (in Kombination mit Prednison / Prednisolon) • Chemotherapie, wenn der reduzierte Allgemeinzustand vor allem auf das metastasierte Prostatakarzinom zurückzuführen ist • Enzalutamid • Radium-223 bei ossärer Metastasierung • Steroide (Dexamethason, Prednisolon, Prednison)	
Level of Evidence 4	Expertenkonsens basierend auf [764-766; 768; 768; 792]	
	Gesamtabstimmung: 95 %	

<u>Zweitlinientherapie</u>

- Zweitlinientherapie nach Docetaxel

6.40	Evidenzbasierte Empfehlung	spezifiziert 2018
Empfehlungsgrad A	Patienten mit kastrationsresistenter, progredienter Erkrankung und gutem Allgemeinzustand nach Chemotherapie mit Docetaxel soll eine der folgenden Therapieoptionen, bei Bedarf in Kombination mit symptombezogener und supportiver Therapie, angeboten werden: (alphabetische Reihenfolge) • Abirateron (in Kombination mit Prednison / Prednisolon) • Cabazitaxel • Enzalutamid Radionuklidtherapie mit Radium-223 bei ossärer Metastasierung Zur Differenzialtherapie siehe Empfehlungen 6.41-6.43.	
Level of Evidence 1+	Literatur: [792; 795-802]	
	Gesamtabstimmung: 100 %	

6.41	Evidenzbasierte Empfehlung	spezifiziert 2018
Empfehlungsgrad 0	Patienten mit kastrationsresistenter, progredienter Erkrankung und gutem Allgemeinzustand nach Chemotherapie mit Docetaxel kann (alphabetische Reihenfolge) · Abirateron (in Kombination mit Prednison / Prednisolon) oder · Enzalutamid angeboten werden. In der jeweiligen Zulassungsstudie wurde eine Verlängerung der Überlebenszeit gezeigt.	
Level of Evidence 1+	Literatur: Abirateron: [795; 796] Enzalutamid [798]	
	Gesamtabstimmung: 100 %	

6.42	Evidenzbasierte Empfehlung	spezifiziert 2018
Empfehlungsgrad 0	Patienten mit kastrationsresistenter, progredienter Erkrankung und gutem Allgemeinzustand nach Chemotherapie mit Docetaxel kann Cabazitaxel angeboten werden. In der Zulassungsstudie wurde eine Verlängerung der Überlebenszeit gezeigt.	
Level of Evidence 1+	Literatur: [799]	
	Gesamtabstimmung: 100 %	

6.43	Evidenzbasierte Empfehlung	geprüft 2018
Empfehlungsgrad 0	Patienten mit kastrationsresistenter, progredienter Erkrankung und gutem Allgemeinzustand nach Chemotherapie mit Docetaxel kann Radium-223 bei ossären Metastasen angeboten werden. In der Zulassungsstudie wurde eine Verlängerung der Überlebenszeit gezeigt.	
Level of Evidence 1+	Literatur: [792]	
	Gesamtabstimmung: 93 %	

6.44	Evidenzbasierte Empfehlung	spezifiziert 2018
Empfehlungsgrad 0	Patienten mit kastrationsresistenter, progredienter Erkrankung nach Chemotherapie mit Docetaxel und reduziertem Allgemeinzustand (ECOG ≥ 2, Karnofsky < 70) kann zusätzlich zur symptombezogenen Therapie eine der folgenden Therapieoptionen angeboten werden: (alphabetische Reihenfolge) • Abirateron (in Kombination mit Prednison / Prednisolon) • Chemotherapie, wenn der reduzierte Allgemeinzustand vor allem auf das metastasierte Prostatakarzinom zurückzuführen ist • Enzalutamid • Radionuklidtherapie mit Radium-223 bei ossärer Metastasierung • Steroide (Dexamethason, Prednisolon, Prednison)	
Level of Evidence 4	Expertenkonsens basierend auf Referenzen zu 6.43 und [99; 173; 803].	
	Gesamtabstimmung: 98 %	

6.45	Evidenzbasierte Empfehlung	neu 2018
Empfehlungsgrad 0	Für Patienten mit kastrationsresistenter, progredienter Erkrankung in gutem Allgemeinzustand kann nach Ausschöpfen der empfohlenen Therapieoptionen (siehe Empfehlung 6.40) ein Therapieversuch mit Lutetium-177-PSMA auf Basis der Empfehlung einer interdisziplinären Tumorkonferenz angeboten werden.	
Level of Evidence 3	Literatur: [804-811]	
	Gesamtabstimmung: 93 %	

- Zweitlinientherapie nach Androgenrezeptor-gerichteter Behandlung

6.46	Evidenzbasierte Empfehlung	spezifiziert 2018
Empfehlungsgrad 0	Patienten mit kastrationsresistenter, progredienter Erkrankung und gutem Allgemeinzustand nach Androgenrezeptor-gerichteter Erstlinientherapie kann eine Sequenztherapie unter Verwendung eines der anderen wirksamen Arzneimittel (siehe Empfehlung 6.40) angeboten werden.	
Level of Evidence 4	Expertenkonsens	
	Gesamtabstimmung: 100 %	

Therapie von Knochenmetastasen

6.47	Evidenzbasierte Empfehlung	modifiziert 2018
Empfehlungsgrad A	Die Therapie symptomatischer ossärer Metastasen ist Bestandteil des onkologischen Gesamtkonzeptes (siehe Empfehlungen 6.37, 6.39, 6.40, 6.43, 6.44). Patienten mit ossären Metastasen soll zusätzlich eine oder mehrere der folgenden Therapieoptionen angeboten werden: · medikamentöse Schmerztherapie · lokale Bestrahlung, siehe Empfehlung 6.48 · operative Intervention (in der Regel in Kombination mit Bestrahlung).	
Level of Evidence bei den jeweiligen Empfehlungen	Literatur: [792; 823; 824]	
	Gesamtabstimmung: 86 %	

6.48	Evidenzbasierte Empfehlung	geprüft 2018
Empfehlungsgrad A	Die lokale perkutane Bestrahlung soll bei Knochenmetastasen in folgenden Situationen eingesetzt werden: • Persistierende lokalisierte Knochenschmerzen • drohende spinale Kompression (ggf. nach operativer Intervention) • nach operativer Stabilisierung • erhöhtes Frakturrisiko	
Level of Evidence 1++	Literatur: [823]	
	Gesamtabstimmung: 97 %	

6.49	Evidenzbasierte Empfehlung	geprüft 2018
Empfehlungsgrad 0	Radionuklide können bei multiplen Knochenmetastasen im kastrationsresistenten Stadium zur Schmerztherapie eingesetzt werden. Die Therapie mit Radium-223 führt bei Patienten in gutem Allgemeinzustand (ECOG ≤ 2) ohne Nachweis viszeraler Metastasen zu einer Verlängerung der Überlebenszeit.	
Level of Evidence 1+	Literatur: [792; 824]	
	Gesamtabstimmung: 97 %	

6.50	Evidenzbasierte Empfehlung	neu 2018
Empfehlungsgrad B	Zur Prävention von Komplikationen bei Knochenmetastasen im Hormon-naiven Stadium sollten Bisphosphonate nicht eingesetzt werden.	
Statement	Die Wirkung von Denosumab in diesem Stadium kann derzeit nicht beurteilt werden.	
Level of Evidence Zoledronsäure 1+ andere Bisphosphonate, Denosumab 4	Literatur: Zoledronsäure: [738; 825-827] Literatur andere Bisphosphonate, Denosumab: [800; 802; 828]	
	Gesamtabstimmung: 100 %	

6.51	Evidenzbasierte Empfehlung	geprüft 2018
Empfehlungsgrad A	Zur Prävention von Komplikationen bei Knochenmetastasen im kastrationsresistenten Stadium soll der monoklonale Antikörper Denosumab oder als Bisphosphonat Zoledronsäure unter Aufklärung von Nutzen und Schaden angeboten werden.	
Level of Evidence 1+	Literatur: [800; 802]	
	Gesamtabstimmung: 100 %	

6.52	Evidenzbasierte Empfehlung	geprüft 2018
Empfehlungsgrad A	Zur Prävention von Kieferosteonekrosen soll vor der Gabe von Bisphosphonaten oder Denosumab • eine zahnärztliche Untersuchung und die ggf. erforderliche zahnärztliche Sanierung sowie • eine Unterweisung und Motivation des Patienten zu überdurchschnittlicher Mundhygiene stattfinden.	
Level of Evidence 3+	Expertenkonsens basierend auf [800; 829]	
	Gesamtabstimmung: 98 %	

Mottet et al., 2018 [18].

Siehe auch: Cornford et al. 2017 [4].

European Association of Urology (EAU)

Guidelines on prostate cancer

Leitlinienorganisation/Fragestellung

to assist medical professionals in the evidence-based management of PCa

Methodik

Grundlage der Leitlinie

Update: New and relevant evidence has been identified, collated and appraised through a structured assessment of the literature and incorporated in all chapters of the 2018 EAU PCa Guidelines (Databases searched included Medline, EMBASE and the Cochrane Libraries, covering a time frame between June 23rd 2016 and May 10th 2017)

Publications ensuing from SRs have all been peer-reviewed.

Panel composition: The PCa Guidelines Panel consists of an international multidisciplinary group of urologists, radiation oncologists, medical oncologists, radiologists, a pathologist and a patient representative

LoE/GoR

For the 2018 edition of the EAU Guidelines the Guidelines Office have transitioned to a modified GRADE methodology across all 20 guidelines [5,6]. For each recommendation within the guidelines there is an accompanying online strength rating form which addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [7];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [8]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences. The strength rating forms will be available online.

Sonstige methodische Hinweise

The literature for the complete document has been assessed and updated, where relevant. The treatment sections have been completely restructured and evidence summaries and recommendations have been amended throughout the current document.

6.1.5.5. General guidelines for active treatment

Recommendations	Strength rating
Inform patients that no active treatment modality has shown superiority over any other active management options in terms of survival.	Strong
Inform patients that all active treatments have side-effects.	Strong
Surgical treatment	
Inform patients that no surgical approach (open, laparoscopic- or robotic radical prostatectomy) has clearly shown superiority in terms of functional or oncological results.	Strong
Perform an extended lymph node dissection (LND), when a LND is deemed necessary.	Strong
Do not perform nerve sparing surgery when there is a risk of extracapsular extension (based on cT stage, Gleason score, nomogram, multiparametric magnetic resonance imaging).	Strong
Do not offer neoadjuvant androgen deprivation therapy before surgery.	Strong
Radiotherapeutic treatment	
Offer intensity-modulated radiation therapy (IMRT) or volumetric arc external-beam radiotherapy (VMAT) for definitive treatment of PCa by external-beam radiation therapy.	Strong
Only offer moderate hypofractionation (HFX) with IMRT/VMAT, including image-guided radiation therapy to the prostate, to carefully selected patients with localised disease.	Strong
Ensure that moderate HFX adheres to radiotherapy protocols from trials with equivalent outcome and toxicity, i.e. 60 Gy/20 fractions in four weeks or 70 Gy/28 fractions in six weeks.	Strong
Active therapeutic options outside surgery and radiotherapy	
Only offer cryotherapy and high-intensity focused ultrasound within a clinical trial setting.	Strong
Only offer focal therapy within a clinical trial setting.	Strong

Metastatic disease - first-line treatment		
Symptomatic patients	In M1 symptomatic patients, offer immediate systemic treatment to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, extra-skeletal metastasis).	Strong
Asymptomatic patients	In M1 asymptomatic patients, offer immediate systemic treatment to improve survival, defer progression to a symptomatic stage and prevent serious disease progression-related complications.	Strong
	In M1 asymptomatic patients, discuss deferred castration with a well-informed patient since it lowers the treatment side-effects, provided the patient is closely monitored.	Weak
All M1 patients	Offer LHRH antagonists, especially to patients with an impending spinal cord compression or bladder outlet obstruction.	Weak
	In M1 patients treated with a LHRH agonist, offer short-term administration of anti-androgens to reduce the risk of the 'flare-up' phenomenon.	Weak
	Do not offer anti-androgen monotherapy for M1 disease.	Strong
	Offer castration combined with chemotherapy (docetaxel) to all patients whose first presentation is M1 disease and who are fit enough for docetaxel.	Strong
	Offer castration combined with abiraterone acetate + prednisone to all patients whose first presentation is M1 disease and who are fit enough for the regimen.	Strong
	Offer castration alone, with or without an anti-androgen, to patients unfit for, or unwilling to consider, castration combined with docetaxel or abiraterone acetate + prednisone.	Strong
M1 patients receiving intermittent treatment	In asymptomatic M1 patients, only offer intermittent treatment to highly motivated men, with a major PSA response after the induction period.	Strong
	• In M1 patients, follow the schedules used in published clinical trials on timing of intermittent treatment. • Stop treatment when the PSA level is < 4 ng/mL after six to seven months of treatment. • Resume treatment when the PSA level is > 10-20 ng/mL (or returned to the initial level of < 20 ng/mL).	Weak
	Do not use castration combined with any local treatment (radiotherapy/surgery) outside an investigational setting except for symptom control.	Strong

6.6.3. *Guidelines for second-line and palliative treatments*

Biochemical recurrence after treatment with curative intent		
Biochemical recurrence after radical prostatectomy (RP)	Offer AS and possibly delayed SRT to patients with a biochemical recurrence (BCR) and favourable prognostic factors (≤ pT3a, time to BCR > three years, PSA-DT > twelve months, GS ≤ 7), who may not benefit from intervention.	Strong
	Treat patients with a PSA rise from the undetectable range with SRT. The total dose of SRT should be at least 66 Gy and should be given early (PSA < 0.5 ng/mL).	Strong
Biochemical recurrence after radiotherapy (RT)	Treat highly selected patients with localised PCa and a histologically proven local recurrence with salvage radical prostatectomy (SRP).	Weak
	Salvage RP should only be performed in experienced centres.	Strong
	Do not offer HIFU, cryosurgical ablation and salvage brachytherapy to patients with proven local recurrence since it is still experimental.	Strong
Systemic salvage treatment	Do not offer ADT to M0 patients with a PSA-DT > twelve months.	Strong

Life-prolonging treatments of castrate-resistant disease		
	Ensure that testosterone levels are confirmed to be < 50 ng/mL, before diagnosing castration-resistant PCa (CRPC).	Strong
	Do not treat patients for non-metastatic CRPC outside of a clinical trial.	Strong
	Counsel, manage and treat patients with metastatic CRPC in a multidisciplinary team.	Strong
	Treat patients with mCRPC with life-prolonging agents. Base the choice of first-line treatment on the PS, symptoms, comorbidities, location and extent of disease, patient preference, and on the previous treatment for hormone-sensitive PCa (alphabetical order: abiraterone, docetaxel, enzalutamide, radium-223, sipuleucel-T).	Strong
Cytotoxic treatment of castrate-resistant disease		
	Counsel, manage and treat patients with metastatic castration-resistant PCa (mCRPC) in a multidisciplinary team.	Strong
	Offer patients with mCRPC who are candidates for cytotoxic therapy docetaxel with 75 mg/m^2 every three weeks.	Strong
	In patients with mCRPC and progression following docetaxel chemotherapy offer further life-prolonging treatment options, which include abiraterone, cabazitaxel, enzalutamide and radium-223.	Strong
	Base second-line treatment decisions of mCRPC on pre-treatment performance status, symptoms, patient preference, comorbidities and extent of disease.	Strong

Supportive care of castrate-resistant disease		
	Offer bone protective agents to patients with metastatic castration-resistant PCa (mCRPC) and skeletal metastases to prevent osseous complications.	Strong
	Offer calcium and vitamin D supplementation when prescribing either denosumab or bisphosphonates.	Strong
	Treat painful bone metastases early on with palliative measures such as external beam radiotherapy, and adequate use of analgesics.	Strong
	In patients with spinal cord compression start immediate high-dose corticosteroids and assess for spinal surgery followed by irradiation. Offer radiation therapy alone if surgery is not appropriate.	Strong

ADT=androgen deprivation therapy; AS=active surveillance; BCR=biochemical recurrence; CPRC=castration-resistant prostate cancer; EBRT=external-beam radiation therapy; GS=Gleason score; HDR=high-dose rate; HFX=hypofractionation; HIFU=high-intensity focused ultrasound; IGRT=image-guided radiation therapy; IMRT=intensity-modulated radiation therapy; IPSS=International Prostatic Symptom Score; LDR=low-dose rate; LHRH=luteinizing hormone-releasing hormone; mCRPC=metastatic castration-resistant prostate cancer; mpMRI=multiparametric magnetic resonance imaging; PCa=prostate cancer; (e)PLND=(extended) pelvic lymph node dissection; PS=performance score; PSA=prostate-specific antigen; RP=radical prostatectomy; RT=radiotherapy; SRP=salvage radical prostatectomy; TURP=transurethral resection of the prostate; VMAT=volumetric arc external-beam radiotherapy; WW=watchful waiting.

NICE et al., 2014 [19].

National Institute for Health and Care Excellence (NICE)

Prostate cancer: diagnosis and treatment

Leitlinienorganisation/Fragestellung

This guideline is relevant to all healthcare professionals who come into contact with men with prostate cancer, as well as to the men themselves and their carers.

Methodik

Grundlage der Leitlinie

Key to the development of all NICE guidelines are the relevant professional and patient/carer organisations that register as stakeholders.

This guideline updates and replaces CG58. Any sections of CG58 that have not been amended are integrated within this updated document. Changes in NICE guideline development methodology since 2008 mean the way information is presented may, at times be inconsistent (for example, the style of evidence presentation). Recommendations are marked **[2008]**, **[2014]** or **[new 2014]** to indicate the year of the last evidence review:

- **[2008]** indicates that the evidence has not been updated and reviewed since 2008
- **[2014]** indicates that the evidence has been updated and reviewed but no changes to the 2008 recommendation has been made
- **[new 2014]** indicates that the evidence has been reviewed and a new recommendation has been made.

LoE/GoR

- According to GRADE

Table 2: Descriptions of quality elements of GRADE

Quality element	Description
Limitations	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect
Inconsistency	Inconsistency refers to tan unexplained heterogeneity of results
Indirectness	Indirectness refers so differences in study population, intervention, comparator or outcomes between the available evidence and clinical question
Imprecision	Results are imprecise when studies include relatively few events and when the confidence interval around the effect estimate includes both no effect and appreciable benefit or harm
Publication bias	Publication bias is a systematic underestimate or overestimate of the underlying beneficial or harmful effect due to the selective publication of studies

Table 3: Overall quality of outcome evidence in GRADE

Quality element	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

Metastatic prostate cancer

Hormonal therapy

Offer bilateral orchidectomy to all men with metastatic prostate cancer as an alternative to continuous luteinising hormone-releasing hormone agonist therapy. **[2008]**

Androgen deprived versus combined androgen blockade (CAB)

Do not offer combined androgen blockade as a first-line treatment for men with metastatic prostate cancer. **[2008]**

Anti-androgen monotherapy

For men with metastatic prostate cancer who are willing to accept the adverse impact on overall survival and gynaecomastia in the hope of retaining sexual function, offer anti-androgen monotherapy with bicalutamide[i] (150 mg). **[2008]**

Begin androgen deprivation therapy and stop bicalutamide treatment in men with metastatic prostate cancer who are taking bicalutamide monotherapy and who do not maintain satisfactory sexual function. **[2008]**

Hormone-relapsed prostate cancer

When men with prostate cancer develop biochemical evidence of hormone-relapsed disease, their treatment options should be discussed by the urological cancer MDT with a view to seeking an oncologist and/or specialist palliative care opinion, as appropriate. **[2008]**

Chemotherapy

The recommendations in this section are from Docetaxel for the treatment of hormone-refractory metastatic prostate cancer (NICE technology appraisal guidance 101.:

Docetaxel is recommended, within its licensed indications, as a treatment option for men with hormone-refractory prostate cancer only if their Karnofsky performance-status score is 60% or more. **[2008]**

Update 2014

Offer spinal MRI to men with hormone-relapsed prostate cancer shown to have extensive metastases in the spine (for example, on a bone scan) if they develop any spinal-related symptoms. **[2008]**

Do not routinely offer spinal MRI to all men with hormone-relapsed prostate cancer and known bone metastases. **[2008]**

Bone targeted therapies

Bisphosphonate

Do not offer bisphosphonates to prevent or reduce the complications of bone metastases in men with hormone-relapsed prostate cancer. **[2008]**

Bisphosphonates for pain relief may be considered for men with hormone-relapsed prostate cancer when other treatments (including analgesics and palliative radiotherapy) have failed. Choose the oral or intravenous route of administration according to convenience, tolerability and cost. **[2008]**

Bone-seeking radio-isotopes

Strontium-89 should be considered for men with hormone-relapsed prostate cancer and painful bone metastases, especially those men who are unlikely to receive myelosuppressive chemotherapy. **[2008]**

It is recommended that treatment with docetaxel should be stopped:

- at the completion of planned treatment of up to 10 cycles, or
- if severe adverse events occur, or
- in the presence of progression of disease as evidenced by clinical or laboratory criteria, or by imaging studies. **[2008]**

Repeat cycles of treatment with docetaxel are not recommended if the disease recurs after completion of the planned course of chemotherapy. **[2008]**

Additional systemic treatments

Offer a corticosteroid such as dexamethasone (0.5 mg daily) as third-line hormonal therapy after androgen deprivation therapy and anti-androgen therapy to men with hormone-relapsed prostate cancer. **[2008]**

Imaging

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[i] At the time of publication (January 2014), bicalutamide did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

Palliative care

Offer men with metastatic prostate cancer tailored information and access to specialist urology and palliative care teams to address the specific needs of men with metastatic prostate cancer. Offer them the opportunity to discuss any significant changes in their disease status or symptoms as these occur. **[2008]**

Offer a regular assessment of needs to men with metastatic prostate cancer. **[2008]**

Integrate palliative interventions at any stage into coordinated care, and facilitate any transitions between care settings as smoothly as possible. **[2008]**

Discuss personal preferences for palliative care as early as possible with men with metastatic prostate cancer, their partners and carers. Tailor treatment/care plans accordingly and identify the preferred place of care. **[2008]**

Ensure that palliative care is available when needed and is not limited to the end of life. It should not be restricted to being associated with hospice care. **[2008]**

Virgo et al., 2017 [26].

American Society of Clinical Oncology (ASCO)

Second-Line Hormonal Therapy for Men With Chemotherapy-Naive, Castration-Resistant Prostate Cancer: American Society of Clinical Oncology Provisional Clinical Opinion

Leitlinienorganisation/Fragestellung

This PCO addresses the following main research question: Do second-line hormonal therapies play a role in the treatment of chemotherapy-naive men with CRPC? Subquestions are:

- Should a castrate state be maintained in patients who develop CRPC?
- In chemotherapy-naive patients who develop CRPC and have radiographic evidence of metastases but minimal symptoms (M1a/M1s CRPC), should second-line hormonal therapies be used? If so, which agents are recommended?

(…)

Methodik

Grundlage der Leitlinie

Expert Panel Composition: The ASCO Clinical Practice Guidelines Committee (CPGC) convened an Expert Panel that comprised prostate cancer experts with specific knowledge in and clinical experience with CRPC, including specialists from medical oncology, urologic oncology, radiation oncology, and guideline methodology.

The ASCO CPGC also convened a Consensus Panel, with similar representation to the Expert Panel, tasked with rating agreement with the drafted PCOs by using ASCO's formal consensus-based methodology.This approach is based on the modified Delphi consensus development methodology for providing clinical guidance when available data do not support more traditional and definitive evidence-based recommendations.

Recherche/Suchzeitraum:

- Systematic review of the available evidence (search dates 1985 through October 2016)

LoE/GoR

- Recommendations reflect high, moderate, or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like “must,” “must not,” “should,” and “should not” indicate that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO provides this information on an “as is” basis, and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information or for any errors or omissions.

Research Question 1: Should a castrate state be maintained in patients who develop CRPC?

- PCO 1. For men who develop CRPC despite castrate levels of testosterone:
  - Patients should be maintained in a castrate state indefinitely. This PCO is based on indirect scientific evidence and current understandings of disease progression mechanisms in prostate cancer. A discussion with patients about the limited nature of available scientific evidence and the balance among potential harms, benefits, costs, and patient preferences is essential when planning treatment.
  - A castrate state should be maintained through orchiectomy or pharmacologic castration (eg, luteinizing hormone–releasing hormone [LHRH] agonists/antagonists, antiandrogens).

Research Question 3: In chemotherapy-naïve patients who develop CRPC and have radiographic evidence of metastases but minimal symptoms (M1a/M1s CRPC), should second-line hormonal therapies be used? If so, what agents are recommended?

- PCO 3. After first-line hormonal treatment failure and a discussion with chemotherapy-naive patients about potential harms, benefits, costs, and patient preferences,
  - Abiraterone acetate plus prednisone should be offered because they significantly improved rPFS and OS as well as secondary endpoints, including median time to opiate use, chemotherapy initiation, performance status deterioration, and PSA progression (v prednisone alone). The drugs are also well tolerated.
  - Enzalutamide should be offered because it significantly improves rPFS and OS. Secondary endpoints are also improved, including time to initiation of cytotoxic chemotherapy, risk of a first skeletal-related event, complete or partial soft tissue response, time to PSA progression, time to deterioration in quality of life, and decline in PSA of ≥ 50% from baseline (vs. placebo). The drug is also well tolerated.
  - Alternative treatment options include immunotherapy (sipuleucel-T), chemotherapy (docetaxel and prednisone), and radium-223.[9,11]
  - If none of these therapies can be obtained or tolerated by the patient, other antiandrogens, prednisone, and ketoconazole/ hydrocortisone may be offered because they provide modest clinical benefits in this population, but no survival benefits have been established.
  - Other alternative treatment options include enrollment in a clinical trial and observation.

- o No evidence provides guidance about the optimal order of hormonal therapies after second-line hormonal therapy for patients with M1 CRPC. The panel was unable to come to a consensus about sequencing.
- o Other second-line hormonal therapy options where results from phase III trials are pending are not suggested.
- o Palliative care should be offered to all chemotherapy-naive men with M1 CRPC, particularly to those who exhibit symptoms or decreased quality of life.[20]

Quellen:
9. Basch E, Loblaw DA, Oliver TK, et al: Systemic therapy in men with metastatic castration-resistant prostate cancer: American Society of Clinical Oncology and Cancer Care Ontario clinical practice guideline. J Clin Oncol 32:3436-3448, 2014
11. Kantoff PW, Higano CS, Shore ND, et al: Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 363:411-422, 2010
20. Ferrell BR, Temel JS, Temin S, et al: Integration of palliative care into standard oncology care: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 35:96-112, 2017

Department of Health, 2015 [5].

National Clinical Guideline

Diagnosis, staging and treatment of patients with prostate cancer

Leitlinienorganisation/Fragestellung

Patients that are covered by this guideline are:

- Adults (18 years or older) with newly diagnosed prostate cancer
- Adults with metastases arising from prostate cancer.

Methodik

Grundlage der Leitlinie

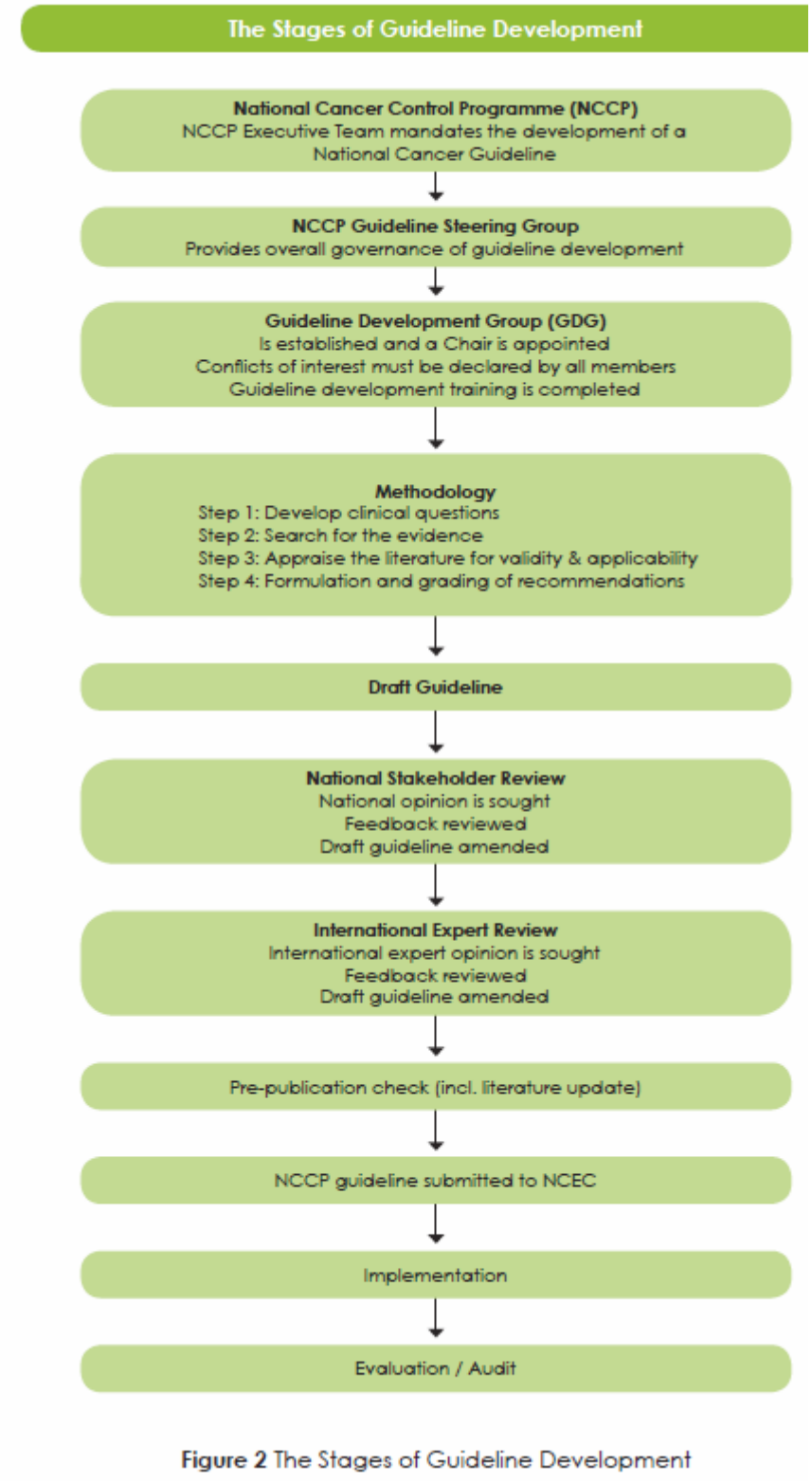

Figure 2 The Stages of Guideline Development

Recherche/Suchzeitraum:

- up to September 2014

LoE/GoR

- The evidence statements and recommendations were then written. Each recommendation was assigned a grade by the GDG. The grade reflected the level of evidence upon which the recommendations were based, the directness of the evidence, and whether further research is likely to change the recommendation.

Table 9 Levels of Evidence for diagnostic studies (Oxford CEBM, 2009)

1a	Systematic review (with homogeneity*) of Level 1 diagnostic studies; clinical decision rule (CDR") with 1b studies from different clinical centres.
1b	Validating** cohort study with good reference standards" " "; or CDR tested within one clinical centre.
1c	Absolute SpPins (specificity) and SnNouts (sensitivity)" ".
2a	Systematic review (with homogeneity*) of Level >2 diagnostic studies.
2b	Exploratory** cohort study with good reference standards; CDR after deviation, or validated only on split-samples§§§ or databases.
3a	Systematic review (with homogeneity*) of 3b and better studies.
3b	Non-consecutive study; or without consistently applied reference standards.
4	Case-control study, poor or non-independent reference standard.
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or first principles.

* By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.

" Clinical Decision Rule (these are algorithms or scoring systems that lead to a prognostic estimation or a diagnostic category).

** Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'.

" " " Good reference standards are independent of the test, and applied blindly or objectively to applied to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study.

" " An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a negative result rules-out the diagnosis.

§§§ Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.

Table 10 Grades of recommendations for diagnostic studies (Oxford CEBM, 2009)

A	Consistent level 1 studies.
B	Consistent level 2 or 3 studies; or Extrapolations from level 1 studies.
C	Level 4 studies; or Extrapolations from level 2 or 3 studies.
D	Level 5 evidence; or Troublingly inconsistent or inconclusive studies of any level.

Extrapolations are where data is used in a situation that has potentially clinically important differences than the original study situation.

Medical oncology

2.7.1.1 The evidence that favours immediate hormone therapy over delayed therapy is not convincing. Therefore, this choice should be made on an individual basis for each patient. Relevant factors include patient preference, the presence of symptoms (i.e. pain), the extent of metastases, PSADT, age, comorbidity, and the effect of treatment on quality of life. **(C)**

2.7.2.1 For patients with biochemical relapse or metastatic recurrence continuous androgen deprivation therapy is the standard option. **(B)**

2.7.2.2 Intermittent androgen deprivation therapy can be considered an acceptable alternative option to be discussed with patients. **(B)**

2.7.3.1 Androgen deprivation therapy should be continued indefinitely in these patients. **(D)**

2.7.4.1 For men with castration resistant prostate cancer, second line hormone therapy should be considered. **(A)**

2.7.4.2 For men with castration resistant prostate cancer in whom chemotherapy is not yet clinically indicated, there is strong clinical data supporting the efficacy of abiraterone (+ prednisone) or enzalutamide. **(A)**

2.7.4.3 For men with castration resistant prostate cancer, whose disease has progressed on or after a docetaxel-based chemotherapy regimen, there is strong clinical data supporting the efficacy of abiraterone (+ prednisone) or enzalutamide. **(A)**

2.7.5.1 Clinicians should offer treatment with abiraterone (+ prednisone), cabazitaxel or enzalutamide to patients with metastatic castration resistant prostate cancer with good performance status who have received prior docetaxel chemotherapy. **(A)**

2.7.5.2 Abiraterone (+ prednisone) or enzalutamide may also be considered in patients who have not received docetaxel. **(A)**

2.7.5.3 Patients with metastatic castration resistant prostate cancer who have predominantly bone metastases may benefit from radium-223. **(A)**

2.7.6.1 For men with castration resistant prostate cancer and bone metastases, treatment with zoledronic acid should be considered. Consider denosumab for men in whom zoledronic acid is contraindicated or not tolerated. **(B)**

Cookson et al., 2015 [2].

Siehe auch: Cookson et al. 2013 [3]

American Urological Association (AUA)

Castration-resistant prostate cancer: AUA guideline amendment

Leitlinienorganisation/Fragestellung

The purpose of this amendment is to incorporate relevant newly published literature to better provide a rational basis for the management of patients with castration-resistant prostate cancer.

Methodik

Grundlage der Leitlinie

The AUA commissioned an independent group to conduct a systematic review and metaanalysis of the published literature on various therapies for CRPC.

Recherche/Suchzeitraum:

- The original systematic review and meta-analysis of the published literature yielded 303 articles published from 1996 through 2013. In April 2014, the CRPC guideline underwent amendment based on a second comprehensive literature search, which retrieved additional studies published between February 2013 and February 2014.

LoE/GoR

- When sufficient evidence existed, the body of evidence for a particular treatment was assigned a strength rating of A (high), B (moderate) or C (low). In the absence of sufficient evidence, additional information is provided as Clinical Principles and Expert Opinions.

Sonstige methodische Hinweise

- Guideline statements based on six index patients developed to represent the most common scenarios encountered in clinical practice were amended appropriately.
  - Asymptomatic or minimally-symptomatic mCRPC without prior docetaxel chemotherapy
  - Symptomatic mCRPC, good performance status, no prior docetaxel chemotherapy
  - Symptomatic mCRPC, poor performance status, no prior docetaxel chemotherapy
  - Symptomatic mCRPC, good performance status, prior docetaxel chemotherapy
  - Symptomatic mCRPC, poor performance status, prior docetaxel chemotherapy

Recommendations:

Asymptomatic or minimally-symptomatic mCRPC without prior docetaxel chemotherapy

This patient represents a common clinical presentation seen in the CRPC setting today. These patients are characterized as having a rising PSA in the setting of castrate levels of testosterone, documented metastatic disease on radiographic imaging and no prior treatment with docetaxel chemotherapy for CRPC. The key distinction between this patient and Index Patients 3 and 4 is symptom status. Specifically, this patient is defined as having no symptoms or mild symptoms attributable to his prostate cancer. However, one must then consider whether the patient requires regular opioid pain medications for symptoms thought to be attributable to documented metastases to achieve this level of pain control. In general, if patients require regular narcotic medications for pain relief, they are not included in this category. Acknowledging these important definitions, the panel makes the following guidelines statements:

- Guideline Statement 5: Clinicians should offer abiraterone plus prednisone, enzalutamide, docetaxel, or sipuleucel-T to patients with asymptomatic or minimally symptomatic mCRPC with good performance status and no prior docetaxel chemotherapy. (Standard; Evidence Level Grade A [abiraterone plus prednisone and enzalutamide] / B [docetaxel and sipuleucel-T])
- Guideline Statement 6: Clinicians may offer first- generation anti-androgen therapy, ketoconazole plus steroid or observation to patients with asymptomatic or minimally symptomatic mCRPC with good performance status and no prior docetaxel chemotherapy who do not want or cannot have one of the standard therapies. (Option; Evidence Level Grade C)

Symptomatic mCRPC, good performance status, no prior docetaxel chemotherapy

These patients have a rising PSA in the setting of castrate levels of testosterone, documented symptomatic metastatic disease on radiographic imaging and no prior history of docetaxel chemotherapy for prostate cancer. The definition of symptomatic disease warrants additional explanation to contrast with Index Patient 2. First, the patient must have symptoms that are clearly attributable to the metastatic disease burden, not any other medical condition. Second,

if having pain, the patient should require regular opiate pain medications for symptoms attributable to documented metastases in order to achieve an acceptable level of pain control. If patients require regular narcotic medications for pain relief, then they are symptomatic from their prostate cancer and should be included in this category.

- Guideline Statement 7: Clinicians should offer abiraterone plus prednisone, enzalutamide or docetaxel to patients with symptomatic, mCRPC with good performance status and no prior docetaxel chemotherapy. (Standard; Evidence Level Grade A [abiraterone plus prednisone and enzalutamide] / B [docetaxel])
- Guideline Statement 8: Clinicians may offer ketoconazole plus steroid, mitoxantrone or radionuclide therapy to patients with symptomatic, mCRPC with good performance status and no prior docetaxel chemotherapy who do not want or cannot have one of the standard therapies. (Option; Evidence Level Grade C [ketoconazole] / B [mitoxantrone] / C [radionuclide therapy])
- Guideline Statement 9: Clinicians should offer radium-223 to patients with symptoms from bony metastases from mCRPC with good performance status and no prior docetaxel chemotherapy and without known visceral disease. (Standard; Evidence Level Grade B)
- Guideline Statement 10: Clinicians should not offer treatment with either estramustine or sipuleucel-T to patients with symptomatic, mCRPC with good performance status and no prior docetaxel chemotherapy. (Recommendation; Evidence Level Grade C)

Symptomatic mCRPC, poor performance status, no prior docetaxel chemotherapy

Clinical trials have generally excluded patients with a poor performance status (ECOG 3-4) from participation. Thus, most data regarding management of such patients is extrapolated from randomized trials of eligible patients who had a better performance status, as well as from some smaller trials and registries. Even a Phase 3 clinical trial that was presumptively designed for a population considered "unfit" for docetaxel (ALSYMPCA to evaluate radium-223) still only allowed a performance status of ECOG 0-1. However, treatments with acceptable safety profiles do exist and should be considered, even in poor performance status patients. This is especially true in those patients in whom the poor performance status may be considered to be directly related to the cancer itself and thus whose status might improve with effective treatment. Treatments must be individually tailored in these patients after a careful discussion of risks and benefits with particular attention to patient QOL.

- Guideline Statement 11: Clinicians may offer treatment with abiraterone plus prednisone or enzalutamide to patients with symptomatic, mCRPC with poor performance status and no prior docetaxel chemotherapy. (Option; Evidence Level Grade C)
- Guideline Statement 12: Clinicians may offer treatment with ketoconazole plus steroid or radionuclide therapy to patients with symptomatic, mCRPC with poor performance status and no prior docetaxel chemotherapy who are unable or unwilling to receive abiraterone plus prednisone or enzalutamide. (Option; Evidence Level Grade C)
- Guideline Statement 13: Clinicians may offer docetaxel or mitoxantrone chemotherapy to patients with symptomatic mCRPC with poor performance status and no prior docetaxel chemotherapy in select cases, specifically when the performance status is directly related to the cancer. (Expert Opinion)
- Guideline Statement 14: Clinicians may offer radium-223 to patients with symptoms from bony metastases from mCRPC with poor performance status and no prior docetaxel chemotherapy and without known visceral disease in select cases, specifically when the

performance status is directly related to symptoms related to bone metastases. (Expert Opinion)

- Guideline Statement 15: Clinicians should not offer sipuleucel-T to patients with symptomatic, mCRPC with poor performance status and no prior docetaxel chemotherapy. (Recommendation; Evidence Level Grade C)

Symptomatic mCRPC, good performance status, prior docetaxel chemotherapy

As patients with prostate cancer receive hormonal therapy earlier in the course of the disease (frequently for non-metastatic disease), they may actually develop castration-resistant disease (based on serologic progression) with non-metastatic or asymptomatic metastatic disease. Thus, additional agents, including docetaxel chemotherapy may be administered earlier in the course of metastatic disease. These trends have resulted in a population of mCRPC patients who have completed docetaxel and may continue to be asymptomatic or minimally-symptomatic with an excellent performance status. While such patients may be healthy enough to receive a number of subsequent therapies, a focus of therapy should also be to maintain their excellent performance status without significant toxicity from additional therapy. It is in this context that providers should choose from a number of additional therapies to offer to this patient population.

- Guideline Statement 16: Clinicians should offer treatment with abiraterone plus prednisone, cabazitaxel or enzalutamide to patients with mCRPC with good performance status who received prior docetaxel chemotherapy. If the patient received abiraterone plus prednisone prior to docetaxel chemotherapy, they should be offered cabazitaxel or enzalutamide. (Standard; Evidence Level Grade A [abiraterone] / B [cabazitaxel] / A [enzalutamide])
- Guideline Statement 17: Clinicians may offer ketoconazole plus steroid to patients with mCRPC with good performance status who received prior docetaxel if abiraterone plus prednisone, cabazitaxel or enzalutamide is unavailable. (Option; Evidence Level Grade C)
- Guideline Statement 18: Clinicians may offer retreatment with docetaxel to patients with mCRPC with good performance status who were benefitting at the time of discontinuation (due to reversible side effects) of docetaxel chemotherapy. (Option; Evidence Level Grade C)
- Guideline Statement 19: Clinicians should offer radium-223 to patients with symptoms from bony metastases from mCRPC with good performance status who received prior docetaxel chemotherapy and without known visceral disease. (Standard; Evidence Level Grade B)

Symptomatic mCRPC, poor performance status, prior docetaxel chemotherapy

The American Society of Clinical Oncology (ASCO) has posted recommendations regarding treatment for patients with advanced solid tumors; particularly in the last months of life. ASCO advocates for an increasing emphasis on a patient's QOL and concentrates on symptom management. Treatment given in the last months of life may delay access to end of life care, increase costs and add unnecessary symptom management. Patients with poor performance status (ECOG 3 or 4) should not be offered further treatment.

- Guideline Statement 20: Clinicians should offer palliative care to patients with mCRPC with poor performance status who received prior docetaxel chemotherapy. Alternatively, for selected patients, clinicians may offer treatment with abiraterone plus prednisone, enzalutamide, ketoconazole plus steroid or radionuclide therapy. (Expert Opinion)

- Guideline Statement 21: Clinicians should not offer systemic chemotherapy or immunotherapy to patients with mCRPC with poor performance status who received prior docetaxel chemotherapy. (Expert Opinion)

Guideline Statements on Bone Health (not specific to any one index patient)

Several factors conspire to place the average patient with metastatic prostate cancer at a higher risk of bone complications. First, the median age of onset of the disease is in the late 60s, meaning that the average patient with metastatic disease may be in the 70s (or beyond), clearly a population at risk of physiologic, age-related decreases in bone mineral density. Secondly, a primary therapeutic intervention in patients with recurrent disease (i.e., ADT) is associated with progressive loss of bone mineral density, not infrequently to the point of measurable osteopenia or frank osteoporosis, increasing the patient's fracture risk, even in patients with non-metastatic disease.54-55 Finally, in patients with advanced disease, bones are the most common site of metastatic disease, with as many as 70% of patients at some point in their course demonstrating evidence of disease in this site.

- Guideline Statement 22: Clinicians should offer preventative treatment (e.g. supplemental calcium, vitamin D) for fractures and skeletal related events to CRPC patients. (Recommendation; Evidence Level Grade C)
- Guideline Statement 23: Clinicians may choose either denosumab or zoledronic acid when selecting a preventative treatment for skeletal related events for mCRPC patients with bony metastases. (Option; Evidence Level Grade C)

Alberta Provincial Genitourinary Tumour Team, 2015 [1].

Prostate Cancer (Version 6)

Leitlinienorganisation/Fragestellung

to describe the appropriate management and follow up strategies for prostate cancer.

Methodik

Grundlage der Leitlinie

This guideline was reviewed and endorsed by the Alberta Provincial Genitourinary Tumour Team. Members of the Alberta Provincial Genitourinary Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Genitourinary Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Unit

Recherche/Suchzeitraum:

- This guideline was originally developed in January, 2005. This guideline was revised in January 2009, January 2011, September 2013, and October 2014 and March 2015.

LoE/GoR

- Similar to the American Society of Clinical Oncology (ASCO) methodology for formulating guideline recommendations, no formal rating schemes for describing the strength of the recommendations are used. They rather describe, in conventional and explicit language,

the type and quality of the research and existing guidelines that were taken into consideration when formulating the recommendations including:

- Description of all known benefits and possible harms
- Evidence summary, quality/quantity/consistency of discussion
- Discussion of the role of clinical experience, theory, values and opinions in developing the recommendation

Stage M+ Castrate Resistant Disease (Indications include symptomatic disease or asymptomatic metastatic disease)

Management

- The benefits of treatment are primarily palliative and related to quality of life, although some systemic therapies confer a small survival advantage.

Palliative Radiotherapy

- EBRT to symptomatic sites
- Strontium 89 (Metastron®) not recommended for routine use, but available for appropriate indications, including:
  - Multiple painful sites of bone metastases on both sides of diaphragm
  - Patient and/or tumor factors contraindicating the use of multiple fields of EBRT for palliation
  - Adequate bone marrow reserve (NB: Platelet count > 100)
  - No evidence of impending spinal cord compression
- No plans for systemic chemotherapy

Systemic Therapy: Clinical trials should be given first consideration where appropriate. Currently, there is no data to support one of these agents/sequences over the other.

- 1st line options:
  - Abiraterone acetate 1g oral daily in combination with prednisone 5 mg oral twice daily (COUGAR 302) can be used prior to docetaxel.(54,55)
  - Docetaxel 75mg/m^2 IV every 3 weeks in combination with prednisone at a dose of 5 mg twice daily.[54]
  - Enzalutimide (pending approval by Health Canada) (PREVAIL).(56)
- 2nd line options:
  - Post progression on docetaxel chemotherapy:
    - Abiraterone acetate[55] or enzalutamide (AFFIRM).(57,58)
    - Cabazitaxel 25mg/m^2 IV every 3 weeks in combination with prednisone 10 mg oral daily.[56]
    - Radium 223 can be given to patients with symptomatic bony metastatic CRPC without visceral metastases (ALSYMPCA).(59,60) Ra 223 is administered upon referral to nuclear medicine and given at a dose of 50 kBq (1.35 microcurie) per kg body weight at 4 week intervals for a total of 6 injections. Funding is currently being sought.
      - Patient selection is important. These patients should be discussed in multidisciplinary tumor board rounds.
  - Post progression on Abiraterone or Enzalutamide
    - Docetaxel chemotherapy
- Subsequent lines:
  - Sequencing with another agent listed above not previously used. For example, abiraterone → docetaxel → enzalutamide → cabazitaxel is a reasonable sequence. There are many others. There is no data to suggest the preferred sequence.
  - Docetaxel rechallenge or Mitoxantrone 12mg/m^2 every 3 weeks in combination with prednisone 5 mg oral twice a day may provide palliation.
  - Sipuleucel-T is not Health Canada approved
- Mitoxantrone 12mg/m^2 every 3 weeks in combination with prednisone 5 mg oral twice a day can provide adequate palliation in 2nd or subsequent line.
- Bone targeted therapy: treatment with bisphosphonates bone targeted agents will be discussed below for patients with metastatic castrate resistant prostate cancer.
- It is important to note that chemotherapy is NOT indicated in patients without evidence of metastatic disease on imaging whose only have manifestation of hormone insensitive disease is a rising PSA.

Bone Health

All patients should ensure adequate calcium and vitamin D intake, using supplements if necessary.

- Metastatic patients, castrate resistant:
  - For patients with castrate resistant and evidence of bony metastatic disease, zoledronic acid 4 mg IV every 4 weeks(74) or denosumab 120 mg subcutaneously every 4 weeks.(77) Zoledronic acid can be considered for reduction in SREs.
  - Denosumab has demonstrated non-inferiority and superiority over zoledronic acid in prevention of SREs and can/should be considered as the first line option.(77) There is no documented survival benefit noted with either of these agents.
  - Dosing of zoledronic acid should be tailored to the patient's kidney function (starting dose to be based on creatinine clearance as per the CPS).
  - Patients should be continuously monitored to ensure adequate renal function.

- If patient clinic condition deteriorates and severe pain develops (narcotic analgesics are required) the routine administration of zoledronic acid bone targeted agents should be reviewed and potentially stopped.
- Osteonecrosis of the jaw has and hypocalcemia have been reported in association with the administration of zoledronic acid. Patients have to be monitored and with the appropriate precautions these complications can be prevented or managed in a timely fashion.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews) am 08.08.2018

#	Suchfrage
1	[mh “Prostatic Neoplasms, Castration-Resistant”]
2	(prostate or prostatic):ti,ab,kw and (cancer* or tumor* or tumour* or carcinoma* or neoplasm* or adenocarcinoma*):ti,ab,kw
3	(resistant or resistance):ti,ab,kw and (castrate or castration):ti,ab,kw
4	(CRPC):ti,ab,kw
5	(#2 and #3) or #4
6	#5 with Cochrane Library publication date from Aug 2013 to Aug 2018

SR, HTAs in Medline (PubMed) am 08.08.2018

#	Suchfrage
1	Prostatic Neoplasms, Castration-Resistant[mh]
2	(prostate[tiab]) OR prostatic[tiab]
3	(((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplasm*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]
4	(castrate[tiab] OR castration[tiab]) AND resistant[tiab] OR resistance[tiab]
5	CRPC[tiab]
6	#1 OR (#2 AND #3 AND #4) OR #5
7	(#6) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))
8	((#7) AND ("2013/08/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 08.08.2018

#	Suchfrage
1	Prostatic Neoplasms, Castration-Resistant[mh]
2	(prostate[tiab]) OR prostatic[tiab]
3	(((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplasm*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]
4	(castrate[tiab] OR castration[tiab]) AND resistant[tiab] OR resistance[tiab]
5	CRPC[tiab]
6	#1 OR (#2 AND #3 AND #4) OR #5
7	(#6) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR*

#	Suchfrage
	recommendation[ti])*
8	(((#7) AND ("2013/08/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]))

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